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THE SIGNIFICANCE OF THE INCUBATION PERIOD IN INFECTIOUS DISEASES.[1]

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MICROBIOLOGY, the study of microorganisms, is a very wide term to use for the description of a department in the John Curtin School of Medical Research. Objections have been raised to the use of "microbiology" instead of the more usual "bacteriology" to describe such a department; but medical microbiology includes the four related sciences of protozoology, mycology, bacteriology and virology. Further, it includes all aspects of the biology of each of these groups of microorganisms: their physiology, their biochemical behaviour, their evolution and genetics, and their ecology—that is, the relations which exist amongst different microorganisms and between them and the higher organisms. From the historical aspect, it is worth remembering that Pasteur himself suggested that the study of microbial life should be designated "*microbie*" or "*microbiologie*", words which he properly regarded as less restricted in meaning than "*bactériologie*" (Dubos, 1950).

The fact that the department of microbiology is part of a school of medical research may be thought to imply some limitation of interest, perhaps to microorganisms which cause disease by direct infection of man. But a little reflection shows that such limitations cannot apply, for who would say that *Penicillium notatum* or *Streptomyces griseus*, the harmless fungi from which the antibiotics penicillin and streptomycin are obtained, are not organisms of medical interest? And who can deny the potential importance to medicine of Sonneborn's (1950) investigation on cytoplasmic inheritance in the slipper animalicule, Paramecium, or Beadle's (1945) studies of biochemical genetics in the bread mould, Neurospora?

Within the wide field of microbiology our department will have to confine its attention to some small, uncultivated but, let us hope, fertile areas. But, as my theme for this evening's lecture will show, there are occasions when one can with profit survey the field widely, and draw examples equally from the viruses, the bacteria and the protozoa.

The study of disease processes passes through several stages. The first is purely descriptive, and many of the most important diseases of mankind have not yet passed this stage of investigation. A new approach is initiated by the determination of the ætiology of a disease. In most of the infectious diseases the causative agent has been established, and investigation can proceed to the third phase, the study of the pathogenesis. Pathogenesis can be investigated at two levels, the "macroscopic"—or the distribution of the infectious agent through the host organism and the reaction of the host as a whole to this invasion—and the "microscopic"—or the interaction of parasite and host at the cellular level. The final stage in the study of the disease process is the elucidation of the parasite-host reaction at the molecular level, the study of the biochemical lesions resulting from invasion of the host by the infectious agent. Tonight I will concern myself with the third stage, that of the pathogenesis of infectious diseases, although in some of the infections I mention knowledge of the ætiology is still incomplete.

[1] The inaugural lecture of the Professor of Microbiology, delivered on August 17, 1950, at Canberra.

Infectious disease is a manifestation of the interaction between host, which may vary in complexity from a bacterium to man, and parasite, which may belong to any one of the four groups of microorganisms I mentioned earlier, or may be a worm or even an insect. The common infectious diseases of man in communities such as our own are expressions of the interaction between man and bacteria or viruses. In all such diseases there is an interval between the exposure of a susceptible host to the infecting agent and the onset of the symptoms of disease. This interval is commonly called the incubation period of the disease and may vary from a few hours to several weeks in duration. In any particular disease, however, its length is relatively constant and predictable. In defining the incubation period, both the moment of infection and the sign or symptom taken as indicating the onset of illness must be defined. In experimental infections of animals the moment of infection is known; but in human diseases reliance must be placed on the observation of subjects with a short and only possible exposure to infection. Such cases were well exploited by Dr. W. N. Pickles (1939), the country doctor of the Yorkshire dales. On the other hand, we can define the onset of symptoms in man as the first feeling of illness, while in animals it must depend upon some easily observed sign, as we are in no position to assess their symptoms. It is apparent that the accuracy of definition of the incubation period is greatly influenced by the insidious or abrupt nature of the onset of illness. In many cases of tuberculosis, for example, it is impossible to define the time of onset at all accurately, while in most of the acute fevers the onset can be determined with considerable precision.

Having decided upon the starting and finishing points for the incubation period, we find that it is not an absolutely constant interval, but varies somewhat. Table I shows the way in which the incubation period varies in a virus disease of mice called mousepox, firstly according to the criterion used to indicate the end of the incubation period, and secondly from animal to animal in any one group. In the experiment upon which the upper part of this table was based, large numbers of mice were exposed to an infected environment for a period of twenty-four hours, and then removed from contact with the virus—the "short and only possible" exposure of the human epidemiologist. It is apparent that even when a fixed point is taken as the end of the incubation period there is some variability in its length, and in the experiment I have just mentioned the extremes observed in the first category on the table—that is, to the appearance of the primary lesion—were four and ten days.

In natural infections such as this the variation in the length of the incubation period may be due, in part, to variation in the size of the infecting dose of microorganisms. But this is not the only cause of the variation, for it is found even when a known small dose is inoculated directly into the tissues, as is apparent from the second part of Table I. This variation is an indication that we are dealing, not with a simple chemical reaction, but with two interacting and varying biological systems, parasite and host.

In text-books on microbiology and on medicine, the most that one can find about the incubation period is that it is the interval of time required for the multiplication of bacteria (or viruses) to take place until sufficient numbers have accumulated to cause noticeable physiological disturbance. However, this seems an inadequate explanation of the fact that the incubation period in streptococcal sore throat is about two days and in typhoid fever about two weeks, for when grown in the test-tube both the streptococcus and the typhoid bacillus multiply with equal speed. And in the common exanthems of childhood the incubation period is still more mysterious, for between known exposure to chicken-pox, for example, and the onset of disease, and a widespread rash, a constant interval of three weeks elapses, during which the infected child is perfectly healthy. I will devote the rest of this lecture to a consideration of what happens during this incubation period, and why it is relatively constant in any particular disease and varies so greatly between one disease and another.

The first important distinction to be made in any consideration of the incubation period is between diseases in which the parasite remains localized at the portal of entry and diseases in which it is distributed throughout the body. As will become apparent as I proceed, this is a more important distinction than the exact type of parasite concerned, whether protozoon, bacterium or virus. We will first consider two diseases, one caused by a bacterium and one by a virus—namely, diphtheria and influenza.

Diphtheria is caused by a bacterium which remains localized on the throat throughout the disease.[1] All the signs and symptoms are due to a soluble toxin produced by the bacterium. Multiplication of the diphtheria bacillus occurs at first in desquamated epithelial cells and surface mucus, and small amounts of soluble toxin are produced. This kills some of the living cells adjoining the multiplying bacteria, and further multiplication proceeds in these, until a grey membrane, containing many millions of bacteria, covers the back of the throat. This membrane sometimes develops within two days of exposure to the infecting agent, and by the time the local lesion can be recognized enough soluble toxin has been produced and spread throughout the body to cause the characteristic toxæmia. Evidence of the damage caused by diphtheria toxin may be found in all organs of the body. The toxin produced by the diphtheria bacillus has recently been purified, and it is a heat-labile protein of very high activity. It seems likely that a single molecule per cell is enough to cause the maximum pharmacological effect. Pappenheimer and Hendee (1947) have suggested that diphtheria toxin interferes in some way with the functioning of cytochrome *b* or some closely related enzyme in the tissues of the susceptible animal. In diphtheria, therefore, there is little mystery about the incubation period of the disease, although there is still a good deal of specula-

[1] This is the orthodox view, but G. Wildführ (*Zentralblatt für Bacteriologie, Parasitenkunde und Infektionskrankheiten (Abteilung* I), Volume CLIV, 1949, page 14) has recently reported a transient bacteriæmia in 28 out of 31 diphtheria contacts who contracted the disease. Diphtheria bacilli disappeared from the circulation before the local throat lesions became obvious.

TABLE I.

The Incubation Period of Mousepox, after Exposure to a Contaminated Environment for Twenty-four Hours, and after Inoculation of a Small Dose of Virus in the Foot. (*From* Fenner, 1948a.)

Number of Mice.	Percentage of Mice Showing as First Evidence of Infection.						
	Not Infected.	Primary Lesion.		Secondary Rash.		Death.	
		Percentage.	Incubation Period.	Percentage.	Incubation Period.	Percentage.	Incubation Period.
60	17	63	6·8±1·7 days	7	11 days	13	8·4±1·4 days
	Dose of Virus Inoculated in Foot.			Incubation Period (to First Swelling of Foot).			
23	500 infective particles			7·2±1·2 days			

tion about what is known by pharmacologists as the incubation period of the action of the toxin. The incubation period of diphtheria is simply the time required for the diphtheria bacilli to multiply sufficiently to produce large amounts of toxin, which causes the throat lesion by its local effect, and by its general effect throughout the body produces the severe intoxication and occasionally the complications characteristic of the disease.

Influenza is a virus disease; that is, it is caused by an agent so small that it will pass through a filter that holds back all bacteria, and so deficient in its own enzyme systems that it will not multiply except in susceptible living cells. In the human being, the natural host of the influenza virus, the only cells which are suitable for its multiplication are those which line the lungs and the upper part of the respiratory tract. In influenza, therefore, virus inhaled by a susceptible host enters these cells of the respiratory tract and multiplies in them. If experiments carried out with chick embryos provide a reliable guide, the amount of virus increases about one hundredfold after an interval of six to ten hours (Henle and Rosenberg, 1949), and is then released by rupture of the infected cells which have been killed by the virus. The newly formed infective particles released from the more central cells are carried upwards towards the bronchi in the sheet of respiratory mucus, and they may infect intact epithelial cells on their way out. Acute toxic symptoms occur two or three days after exposure to the infecting agent. The exact origin of the toxic symptoms of influenza is not clear. Certainly no soluble toxin, like diphtheria toxin, is concerned. However, large doses of influenza virus do cause toxic symptoms when inoculated intravenously or intracerebrally in mice, and it is possible that in man the soluble disintegration products of necrosed cells and virus particles are absorbed into the circulation and cause the symptoms of fever, headache, and so on.

Although the exact cause of the symptoms in terms of the "biochemical lesion" or disturbance of the chemical processes of the cells of the host is not so well understood in influenza as in diphtheria, we can see that as far as the significance of the incubation period is concerned the two infections are closely related. In each the infectious agent is localized to the surface cells, of the throat in diphtheria, and of the throat and adjacent lung in influenza. And in each the incubation period represents the interval between lodgement of the infectious agent and its multiplication at or near the site of lodgement until sufficient numbers accumulate to influence the physiological state of the host. As we survey the infectious diseases we find that this pattern holds for most of the localized acute infectious diseases, be they bacterial or viral in origin, as for example streptococcal sore throat, the common cold, and the bacterial dysenteries. All these diseases have short incubation periods of two to four days between the receipt of the infectious agent and the production of signs and symptoms.

Before we go on to the next section of our discussion, it may be useful to consider briefly the anatomy of the animal body in so far as it concerns us tonight. The body possesses several epithelial surfaces through which infectious agents can enter—namely, the skin, the intestinal mucosa, the throat, and the cells lining the respiratory tract. The tissues just beneath all these surfaces are richly provided with lymphatics which communicate more or less directly with regional lymph nodes, and it is almost impossible for any accumulation of microorganisms to occur in the skin, for example, without some reaching the regional lymph node. These lymph nodes are effective filters, for the entering lymph flows into irregular sinuses, which are lined by phagocytic cells that actively engulf any foreign objects which enter. The lymph is eventually drained from these regional lymph nodes by efferent lymphatics, which lead, through other deeper lymph nodes, to the thoracic duct, which in turn enters directly into the blood-stream. Here again any foreign matter, including microorganisms, which has passed through the lymph node barrier soon enters other filter organs—the spleen, the liver and the bone marrow—in which there is an arrangement of irregular blood sinuses and phagocytic cells similar to the lymph sinuses found in the lymph nodes. An understanding of this barrier or filter system is essential for the proper comprehension of the pathogenesis of generalized infectious diseases.

When we come to consider the diseases in which the infectious agent becomes generalized, the position is quite different from what I have just described in diphtheria and influenza. In the first place, the interval between receipt of the infectious agent and the appearance of symptoms is often quite long, measurable in days instead of hours. And in the second place the predominant signs may not be localized to the site of entry of the infectious agent, as they are, to a large extent, in the diseases we have been considering, but may involve organs in parts of the body far removed from the portal of entry. In the exanthems of childhood, for example, the viruses enter the body through the upper part of the respiratory tract; but the most obvious sign of the disease may be a generalized rash which develops two or three weeks later.

Our study of the significance of the incubation period in these generalized diseases is considerably simplified if we use model diseases of small laboratory animals. We will take smallpox, with an incubation period of twelve days to the first symptoms and fifteen days to the rash, as our example of a generalized virus disease, and typhoid fever, with an incubation period of about twelve days, as our example of a generalized bacterial disease. While it is possible to grow the virus of smallpox and the typhoid bacillus outside the human body, and to count the numbers of microorganisms in a suspension, it is difficult to carry out investigations on the distribution of the infectious agents during the silent incubation period, for we do not know then who is infected. We are fortunate in having two natural infections of mice which can be used, with certain limitations, as models of smallpox and typhoid fever. Mice can be infected by the "natural" route with known small numbers of the virus or bacterium, and by killing infected mice at regular intervals after their infection and counting the numbers of the infectious agent in various organs we can find out how they are distributed through the body.

The mouse diseases in question are mousepox and mouse typhoid. Mousepox is caused by a virus which is closely related in size and chemical nature to the smallpox virus, and the disease it causes resembles smallpox in two important characteristics: there is a relatively long incubation period of seven to eight days, and in animals which survive the acute infection a rash appears a couple of days after the end of the incubation period (Fenner, 1949*b*).

As the natural portal of entry of the virus of mousepox is through small abrasions of the skin, large numbers of mice were inoculated in the pad of the foot with a known small dose of virus and killed at various intervals after infection (Fenner, 1948*b*). The numbers of virus particles in different organ suspensions were determined by the inoculation of chick embryos and mice, and it was possible to construct graphs showing the relationship for a number of organs between virus content and time.

When we consider the information thus obtained on the spread of the virus through the mouse body, and supplement it with more detailed and frequent studies during the first few hours after infection, it is possible to interpret the results as shown in Figure I. It is important to realize, when we compare this with the localized diseases I described earlier—diphtheria and influenza—that everything shown in the diagram occurs during the incubation period. It is apparent that here we are concerned, not only with continued local multiplication of virus, but with a stepwise multiplication and invasion: multiplication which penetrates in turn the various protective barriers—lymph node and spleen-liver-bone marrow—to produce the free circulation of virus in the blood, which is followed by widespread infection of the epithelial cells of the skin. Infection of the latter cells is far advanced at the end of the incubation period, as histological study clearly shows, and the lesions of the rash appear a few days later. The incubation period, far from being occupied only by local multiplication of virus, is here the most important and vital phase of the disease. The stage of symptoms is to a large extent merely the foregone

conclusion of the dispositions and concentrations of the virus particles which have been effected during the incubation period.

Before discussing the implications of this interpretation, I will describe the results of similar investigations made in Denmark some years ago, with the laboratory model of typhoid fever, called mouse typhoid (for a summary in English, see Madsen, 1937). Just as mousepox is caused by a virus related to smallpox virus, and resembles smallpox in its basic clinical features, so mouse typhoid is caused by a bacterium closely related to the human typhoid bacillus. Like human typhoid, the portal of entry is the intestinal tract. The incubation period, from ingestion of the bacteria until the loss of normal activity which is the first sign of infection, is about

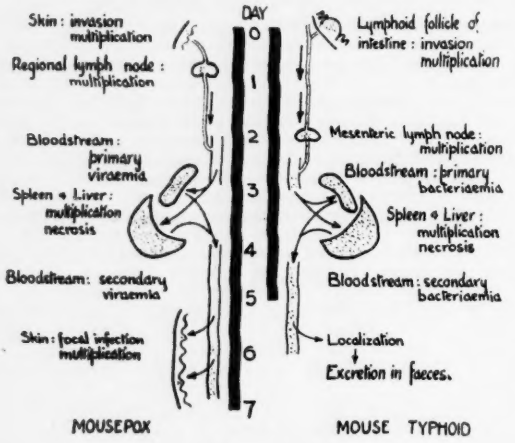

FIGURE I.

Diagrammatic representation of the sequence of events during the incubation period of mousepox (after Fenner, 1948*b*) (left); and of mouse typhoid (from data of Jensen, 1929) (right). The vertical black bars indicate the lengths of the incubation period in the two diseases.

six days. In such details, also, as involvement of the spleen and excretion of the bacteria in the fæces and urine, mouse typhoid is a good model for human typhoid. Jensen (1929) carried out a series of experiments similar to those I have just described in mousepox. He infected a large number of mice by feeding them with ten drops of a culture of mouse typhoid bacilli—an enormous dose, incidentally, which makes direct comparison of his results and those obtained with mousepox a little more difficult. He then made estimates of the numbers of bacteria in different organs during the incubation period and in the period of overt disease.

Some of the ingested bacteria are immediately excreted in the fæces, and others enter the lymphoid follicles of the intestine, and multiply there. By the end of the second day they have passed from the intestinal mucosa to the mesenteric lymph node, where again they multiply and pass through the thoracic duct into the blood-stream. But they can rarely be isolated from the blood at this stage, although they are found in both liver and spleen. The phagocytic cells of these organs perform the same clearing function as in mousepox, but the ingested bacteria are not killed, and proceed to multiply, until a few days later massive bacteriæmia occurs, with subsequent localization of the bacteria in the gall-bladder and elsewhere, and excretion in the fæces. In Figure I the sequence of events during the incubation period of mouse typhoid is compared with the mechanism of infection in mousepox.

Ørskov and his collaborators carried out parallel experiments with several other bacteria and with other experimental animals always with the same type of result, and Meyer has shown that a precisely similar series of events occurs in plague. In generalized infections, whether due to virus, rickettsia or bacterium, the mechanism of infection is the same. It is possible that even in protozoal diseases, such as malaria or kala-azar, the same basic pattern underlies the distribution of the parasite, although the intravenous inoculation of the parasites by the mosquito in malaria may eliminate the first two stages of epithelial and regional lymph node multiplication.

Natural infection is usually due to a very small number of microorganisms, especially in virus diseases, and so there is, firstly, localized multiplication at the portal of entry; then the infectious agents proceed by way of the superficial lymphatics to the regional lymph node, where they are arrested by the phagocytes; then once again they multiply and pass through the thoracic duct to enter the blood-stream. Investigations with vaccinia in rabbits (Yoffey and Sullivan, 1939) suggest that the lymphocytes of the regional lymph node may sometimes act as a disseminating mechanism, carrying virus throughout the body. After the nasal instillation of large doses of virus, these observers found that the regional lymph node did not act as a barrier to further spread of the virus; rather did the latter become attached to lymphocytes and pass out into the efferent lymphatics and thus to the blood-stream.

Just as in the majority of infections the phagocytic cells in the lymph node temporarily arrest the progress of the microorganisms along the lymphatics, so do the phagocytic cells lining the sinuses of liver, spleen and bone marrow extract them from the blood stream (Martin and Kerby, 1950). But in those diseases in which generalization occurs, the phagocytes in both lymph node and the internal organs fail to destroy the infectious agents, which multiply at first in them and then in adjacent parenchymal cells. Eventually the capacity of the clearing mechanism is overcome, and frank bacteriæmia or viræmia occurs. The sequel now depends on several factors, the nature and tissue affinities of the parasite and the effectiveness of the host's antibody response being perhaps the most important. In many diseases, such as mousepox and the childhood exanthems of man, the microorganisms circulating in the blood lodge in the skin, multiply there and cause a rash. In other diseases they become localized in the bone marrow, the gall-bladder, or the urinary bladder, and in still other diseases in the lungs or the brain.

What is the essential difference, then, between the generalized and the localized diseases? It is apparent that in all but the most superficial infections microorganisms must enter the superficial lymphatics, and therefore the regional lymph nodes. This occurs in both of the localized diseases I described earlier, influenza and diphtheria. In some diseases the infecting microorganism is destroyed by these phagocytes, or by those in the next barrier—the liver-spleen-bone marrow. These diseases therefore remain localized, in the skin, or the lungs, or the intestine.[1] We may instance diphtheria, influenza, boils and bacterial dysentery as examples of such localized infections. And in other diseases the infectious agents multiply readily in the phagocytic cells of the lymph nodes and of the liver and spleen, and infect neighbouring parenchymal cells. In these diseases generalization of the infectious agent through the blood-stream is the rule. Consideration of the Salmonella group provides excellent illustrations of both types of disease, for such closely related organisms as *Salmonella enteritidis* and *Salmonella blegdam*, which can be distinguished only with difficulty by the bacteriologist (Baker, Bragdon, Fenner and Jackson, 1949), almost invariably cause localized or generalized infections respectively. *Salmonella enteritidis* is a common cause of diarrhœa and vomiting, and, as we might expect in such a localized infection, the incubation period is usually short, one to three days. On the other hand, *Salmonella blegdam*, like the typhoid bacillus, causes enteric fever, with severe and prolonged fever and symptoms referable to organs far removed from the gastro-intestinal tract. In this generalized disease the incubation period is about fourteen days.

[1] This is an over-simplification. In many localized diseases small numbers of bacteria or virus particles do enter the circulation, gaining access directly from damaged blood vessels of the local lesions. Nevertheless, the microorganisms concerned rarely if ever multiply elsewhere than in the local lesion, in the skin, lung or intestine, as the case may be.

We have earlier defined disease as an interaction between parasite and host. We shall not expect, therefore, that the distinction I have made between generalized and localized infections will be decided only by the nature of the infecting microorganism, for differences in host response must play a part. This is borne out by consideration of both types of infection. Every now and then the staphylococcus, which ordinarily causes only a localized skin infection, overwhelms the defences of the body and causes generalized septicæmia. When this occurs we find that the staphylococcus usually behaves much as did the mouse typhoid bacillus or the mousepox virus. There may be the same stepwise process of infection from local lesion, through lymph node and then internal focus, until generalization in the blood-stream occurs, although sometimes entry to the circulation may be effected directly from damaged blood vessels in the local skin lesions. On the other hand, when experimental infections of mousepox and mouse typhoid are established in actively immunized mice, we find that viral or bacterial multiplication rarely extends beyond the local site of entry of the microorganisms, the skin or the lymphoid follicles of the intestine, as the case may be, and the regional lymph node (Jensen, 1929; Fenner, 1949*a*).

Every infectious agent which gains access to the body, whether to the throat, the lungs, the skin or the intestine, is potentially capable of initiating a generalized infection. Whether it does so or not depends upon the nature of the microorganism, for many microorganisms are unable to multiply in the cells of deeper tissues of the body, and upon the response of the host. Many factors enter into the latter, but the immune state is probably the most important. The rarity of staphylococcal septicæmia in adult life and its frequency in infancy are almost certainly due to the immunization of adults by repeated slight infections, and other examples are provided by the localized multiplication of mousepox virus and typhoid bacilli which I have just described in immunized animals.

I have discussed the differences in pathogenesis of generalized and localized diseases in descriptive terms only. The real problem is to know how it comes about that in some phagocyte-parasite reactions the phagocytes almost invariably suppress multiplication of the parasite, and in others the parasites usually multiply in the phagocytes with little or no hindrance. The attack on this problem must eventually be along chemical lines, and it is inevitable that such a study would not only illuminate cell-parasite interactions, but would also lead to advances in our understanding of the physiology of mammalian cells.

The incubation period in the generalized infections is characteristically long, for the organism has to pass through a series of barriers before final generalization and overt disease occur, and in localized infections the incubation period is usually short, because the symptoms are due to local multiplication and there is no stepwise invasion of internal organs. There are, of course, exceptions to this general statement. When *Mycobacterium ulcerans*[1] the causative organism of the skin ulceration of humans described by McCallum, Tolhurst, Buckle and Sissons (1948), is inoculated into the foot pad of mice in doses consisting of several million organisms, the incubation period of the localized infection which follows is relatively short—about seven days. But when the dose is only five or ten living bacteria the incubation period may be as long as 150 days (Fenner, 1950). In this case the bacterium multiplies very slowly, and signs of the infection do not occur until enormous numbers of organisms have been produced in the site of inoculation.

Apart from such exceptions as the skin ulcers due to *Mycobacterium ulcerans*, and infections like rabies in which there is evidence that spread of virus from the site of infection to the brain occurs by neural pathways, it is reasonable to say that if the incubation period of a disease is long then it is likely that the microorganism has passed through the usual series of barriers (lymph node, spleen, bone marrow and liver) before reaching the organ in which symptoms are produced. Such a concept may be valuable in directing investigations on some of the diseases about which we still know little, especially primary atypical pneumonia and the viral encephalitides. It may be that in these diseases, which have incubation periods of seven to fourteen days, the infecting agent does not remain localized in the lung or proceed directly to the brain by neural pathways; it is possible that instead generalization occurs after the initial superficial infection, and the microbe lodges in the lung or brain from the blood-stream. It might be profitable, therefore, to look for the causative viruses in the blood during the very early stages of the overt disease, paying due regard to the possible presence of specific or non-specific virus-inactivating factors in the serum.

Among the important human virus diseases, there are few in which controversy upon the mechanism of spread of the virus in the body has been greater than poliomyelitis, and there is still no general agreement upon the subject. Recently the same Danish investigators who carried out valuable investigations upon the mechanism of infection with bacteria turned their attention to the mode of spread of the causative virus of a mouse model of poliomyelitis, mouse encephalomyelitis or Theiler's disease. Litters of young mice were infected with Theiler's virus by the oral route (Ørskov and Andersen, 1948). Long before the central nervous system was demonstrably infected, virus was found in the blood, liver and lymph nodes. Contrary to the experience with other bacteria and viruses which cause generalized diseases, however, there was no demonstrable growth of virus in these organs. Quite a different mechanism of infection may be concerned in the diseases caused by these highly neurotropic viruses.

I have omitted from consideration tonight the role of sensitization in the pathogenesis of infectious diseases. While sensitization to bacterial products is of obvious importance in tuberculosis (Rich, 1944), the evidence for its implication as an important factor in determining the length of the incubation periods of the acute infectious diseases is not convincing. Nevertheless we may anticipate increasing evidence of the importance of such host reactions as sensitization in the pathogenesis of the symptoms of a variety of diseases.

Conclusion.

Let me conclude by emphasizing again the basic similarity of the mechanism of infection in all infectious diseases of animals; in all interactions between animal host and microbial parasite, whether the latter be bacterial, viral, protozoal or fungal. We have seen that the duration of the incubation period depends, in general, on the capacity of the parasite (*a*) to produce a lesion by local multiplication, (*b*) to multiply in phagocytes and thus overcome the barriers of lymph node and spleen-liver-bone marrow, and (*c*) on the rate of multiplication of the parasite and what we may call its critical concentration—that is, the degree of multiplication which must occur in any organ before lesions are produced. And we have seen further that these capacities depend primarily on the nature of the parasite, and secondarily on the nature of the host response. Thus, underneath the endless diversity of the symptomatology of the infectious diseases, there is unity in the mechanism of infection, which, with certain exceptions, is essentially the same for the smallest viruses and the largest bacteria.

In every science the accelerating accumulation of new facts sometimes makes the outlook for the investigator and the practitioner disheartening, for it seems that it is beyond the capacity of one individual to grasp them all. But concurrently with this accumulation of new facts it is sometimes possible to perceive a unity underlying them, so that by understanding the basic plan we can dispense with the necessity for remembering isolated facts. The concept which I have elaborated tonight may provide a scaffolding upon which can be hung some of the many and diverse features of infectious disease which are the everyday concern of the health officer and the practitioner of medicine.

[1] This is the name which has been proposed for the new mycobacterium by McCallum, Tolhurst and Buckle (personal communication).

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VENOUS OCCLUSION PLETHYSMOGRAPHY: A CRITICAL STUDY.

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AT the Alfred Hospital, venous occlusion plethysmography has been introduced for the study of circulatory disturbances, and is proving useful in the diagnosis of peripheral vascular diseases, in appraising the value of operations such as sympathectomy directed at improving the blood flow to a part, and in investigating the effect of vasodilator drugs. Although this method has been used extensively in research and has been employed clinically overseas, so far as is known its use has not been reported in Australia. Therefore, it is considered of value to relate briefly the historical development of the procedure, to describe the apparatus being used at this hospital, and to analyse critically possible errors in its use. In a later paper it is intended to illustrate its application in the diagnosis of peripheral vascular diseases.

Venous occlusion plethysmography is a procedure devised to measure the blood flow in the extremities. The limb, or part of it, is fitted in a sealed box containing air or water, which is connected to a recording device so that changes in volume of the enclosed part are registered. The venous return from the limb is occluded for a short time by means of an air-inflated cuff, and the increase in volume of the enclosed part resulting from this is regarded as a measure of the arterial inflow. Knowing the time over which this increase in volume has occurred and the volume of the enclosed part, one can calculate the blood flow in millilitres of blood per 100 millilitres of limb per minute.

Brief Historical Survey.

Plethysmography as a research method has a long history. In 1905 Brodie and Russell established the principles of plethysmographic estimation of the blood flow, and in 1909 Hewlett and Van Zwaluwenburg adapted this method for the estimation of the blood flow through the extremities of man. Lewis and Grant in 1925 described a forearm water plethysmograph. This instrument, with its modifications, has proved of value in studying the physiological responses of the blood vessels and blood flow in different parts in hypertensive states. Thus such an instrument was used by Prinzmetal and Wilson (1936) and by Pickering (1936) in investigating the nature of the peripheral resistance in arterial hypertension. The value of plethysmography in measuring the blood flow in peripheral vascular diseases was demonstrated in 1938 by Kunkel and Stead, who used a water plethysmograph for the foot. Recently there have been numerous reports of investigations by this method. One of the chief workers using it is Abramson (1944), who, with his associates, has studied the peripheral blood flow in various parts of the extremities in numerous conditions and its response to various therapeutic measures.

The workers so far mentioned have used a water plethysmograph, although Abramson (1944) states that his apparatus can also be used for air plethysmography. As the latter method has certain theoretical advantages to be mentioned, it is preferred by some investigators. Thus an air plethysmograph designed by Berry is illustrated in Allen, Barker and Hines's book "Peripheral Vascular Diseases" (1947). Recently Berry and his associates (1948) have described an air plethysmograph which uses compensating spirometers to eliminate errors due to alteration in room temperature and pressure. The experimental error of their method, determined by perfusing the plethysmograph with an experimental schema, was found to be negligible. Also, animal experiments were carried out to uphold the validity of the fundamental principles of plethysmography.

Most workers using this procedure have recorded the volume changes by means of a volume recorder with a pen writing on a moving drum or paper. As there are theoretical objections to this method because of the slowness of response of the recording instrument, more recently a few workers have used an optical recording system, such as described by Wright and Phelps (1940).

Plethysmography has usually been regarded more as a research than as a clinical method. However, Goetz (1948) has devised a portable finger plethysmograph, in which the digit is surrounded by a cuff of air in a glass tube and the volume changes are recorded by an optical system, and has stated that this instrument is of great value in clinical work in determining the presence of absence of arterial obstruction, and whether or not the blood flow is increased by methods producing "reflex" dilatation.

Applications.

Some of the applications of plethysmography will be apparent from the historical survey, but the main uses of this method may be listed more systematically as follows.

1. It has been of value in determining the normal reactions in man of the peripheral blood vessels to physical stimuli.

2. It has proved a useful method in investigating the site of the vascular resistance in hypertensive states.

3. It provides a method of studying the effect on the blood vessels of various chemical agents, both physiological (such as adrenaline and nor-adrenaline) and therapeutic (such as various vasodilator drugs).

4. It is a tool for the clinical investigation of peripheral vascular diseases, allowing a quantitative estimate to be made of the amount of blood flow, and its response to various therapeutic measures such as sympathectomy.

Description of a Procedure of Plethysmography by Means of an Air Plethysmograph.

Apparatus.

As the principle is the same in the operation of all limb plethysmographs, a foot apparatus only will be described, and reference will be made to some special points in the construction of a plethysmograph for the calf. A hand plethysmograph is similar, with modifications in shape and size, to that for the foot, and a forearm instrument to that for the calf.

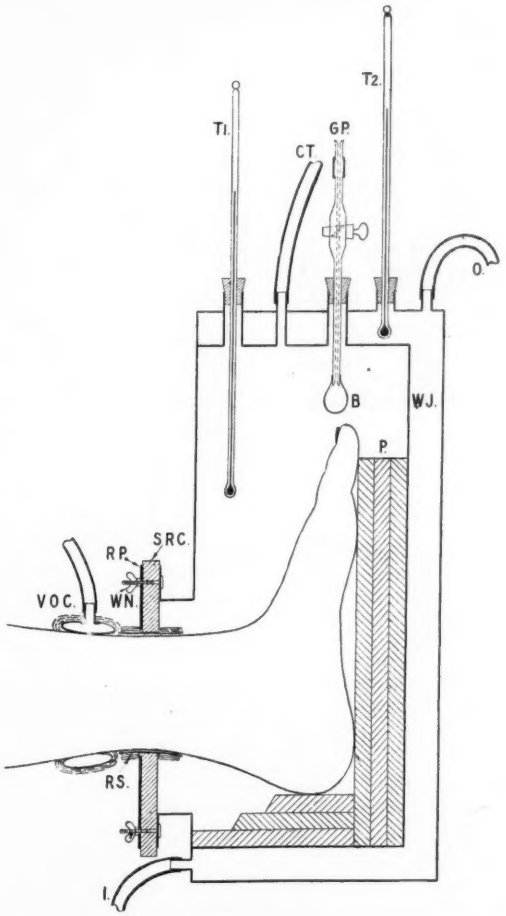

FIGURE I.

Foot plethysmograph. B, balloon; C.T., connecting tube to recording apparatus; G.P., graduating pipette; I, inlet to water jacket; O, outlet from water jacket; P, pad of sponge rubber; R.S., rubber sleeve; R.P., retaining plate; S.R.C., sponge rubber cuff; V.O.C., venous occlusion cuff; W.J., water jacket; W.N., winged nut.

Since air is the usual environment of man, it has been considered that a better indication of the blood flow under physiological conditions would be obtained by the use of an air than of a water plethysmograph. Possible objections to water plethysmography are that the water exerts a pressure on the veins depending in amount on their depth below the surface, and also that the recording of blood flow is slowed because of the inertia of the water.

On the other hand, the temperature of the medium surrounding the limb is more readily controlled when it is water than when it is air. In the present apparatus an attempt has been made to control the temperature of the air in the instrument by surrounding it with a water-jacket.

The principle of construction and dimensions of the foot plethysmograph will be readily followed from Figure I. It consists essentially of a metal box measuring six inches by fourteen inches by five inches, surrounded on five sides by another box, with one inch space between the walls. The various connexions and fittings are sufficiently explained by the diagram. Within the inner box are placed pads for the support of the heel and sole of the foot. A copper collar with a flange projects from the inner box. A sponge rubber cuff with an opening to approximate the lower end of the leg and provided with a thin rubber sleeve of dental dam is fitted on the collar by means of studs and is held in place by two metal retaining plates secured in position by winged nuts. Several sponge rubber cuffs are required to fit legs of different sizes. Details of the construction of that part of the plethysmograph surrounding the lower end of the leg are shown in Figure IA.

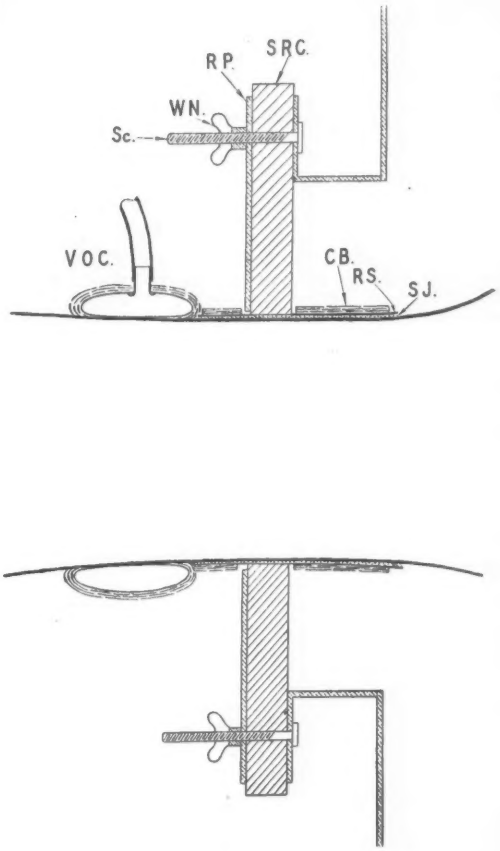

FIGURE IA.

Details of sealing the limb in the foot plethysmograph. C.B., crêpe bandage; R.P., retaining plate; R.S., rubber sleeve; Sc., screw; S.J., surgical jelly; S.R.C., sponge rubber cuff; V.O.C., venous occlusion cuff; W.N., winged nut.

A hot water bath with an electric heating unit is used as a reservoir for water to maintain that in the jacket

at the required temperature. From the bath, a tube leads to the inflow opening of the water jacket, the water being returned via an outflow tube. A Higginson's syringe is inserted in the water circuit to provide means for the circulation of the water.

As the volume of the plethysmograph cannot alter, changes in volume of the foot result in proportionate changes in pressure. These are transmitted to the recording system by pressure tubing 1·75 metres long and of three-millimetre bore. Recording is by an optical method with the use of a Wigger's type of manometer. A glass T-connexion, with a tap which may be opened to the external air, is inserted in the pressure transmission tubing just behind the manometer.

The calibrating device consists of a balloon suspended as shown in the air compartment of the plethysmograph and connected by a tap to a record adapter.

For arterial occlusion distal to the plethysmograph when required, and for venous occlusion, cuffs composed of tubing one and a half inches wide encased in canvas envelopes are used. These are connected by means of pressure tubing to four-gallon air reservoirs. The pressures in the reservoirs are read from mercury manometers. The cuffs can be inflated or deflated very rapidly by means of appropriately arranged taps.

Figure II shows the construction of the calf plethysmograph. It is cylindrical to conform to the shape of the part. Again, the inner air-containing compartment is surrounded by a water jacket. In this case an air-tight seal of the limb is necessary at each end and is accomplished as before by sponge rubber cuffs and thin rubber sleeves, the cuffs being held in position by retaining plates. The latter are specially constructed as illustrated in Figure IIA to allow them to be slipped over the heel.

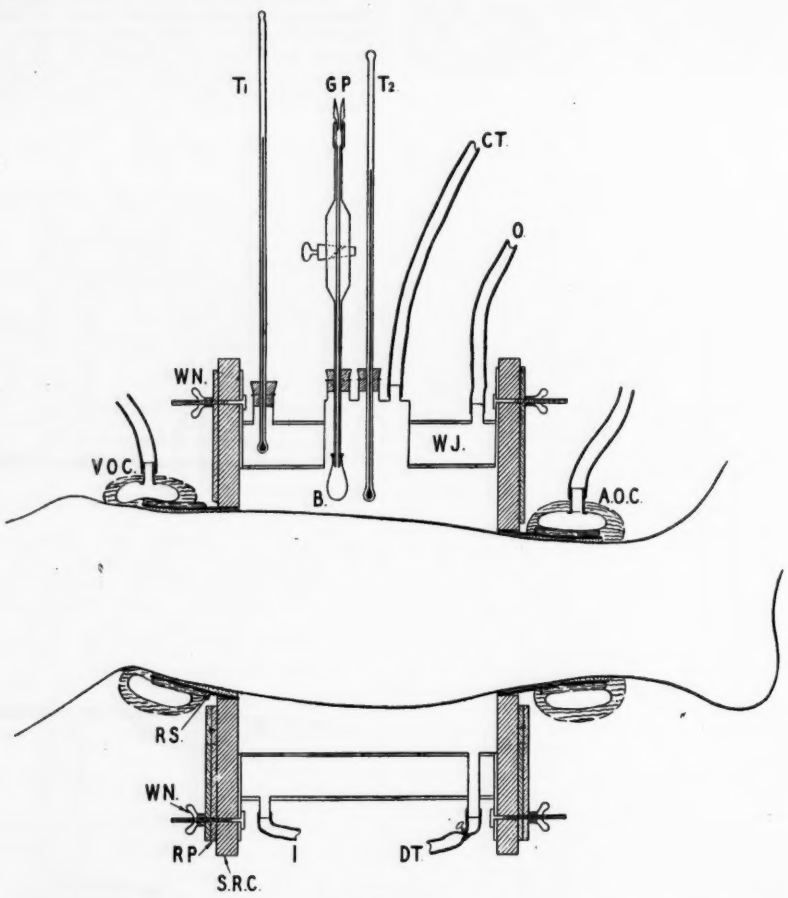

FIGURE II.

Calf plethysmograph. A.O.C., arterial occlusion cuff; B., balloon; C.T., connecting tube to recording apparatus; D.T., drainage tube; G.P., graduating pipette; I., inlet to water jacket; O., outlet from water jacket; R.P., retaining plate; S.R.C., sponge rubber cuff; V.O.C., venous occlusion cuff; W.J., water jacket; W.N., winged nut.

Method.

The method used for foot plethysmography will first be described and, later, modifications in the case of the calf will be briefly mentioned. (The methods for the hand and forearm are similar to those for the foot and calf respectively.)

The temperature of the room in which the observations are carried out is kept as constant as possible, usually about 22° C. The patient should be in the room resting on the bed for at least thirty minutes before the recordings are commenced.

The outer jacket of the plethysmograph is filled with water at 1° C. higher than that required in the air chamber, the latter usually being at about 35° C. The plethysmograph and limb are suitably supported so that the foot is at heart level and the ankle slightly higher

than the knee. The shaved leg is smeared with catheter lubricant just above the ankle and an appropriately sized cuff with its rubber sleeve, similarly lubricated, is fitted, the lower surface of the cuff being six inches above the under surface of the heel. The cuff must fit loosely enough not to cause venous congestion, but the sleeve must fit snugly enough to be air-tight. The sleeve is held in position by a very lightly applied crêpe bandage.

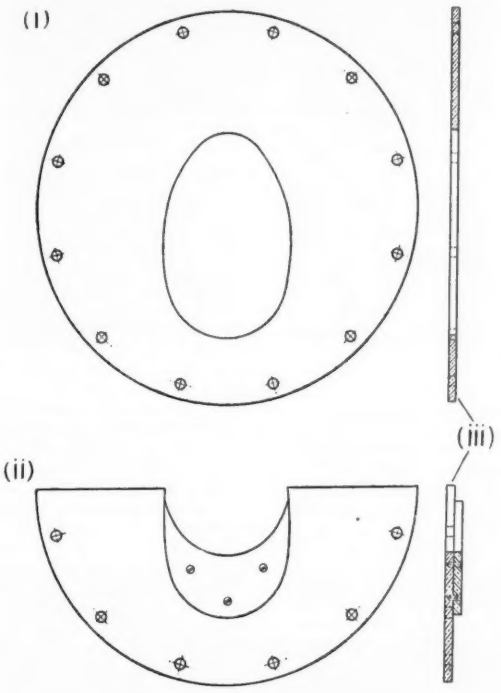

FIGURE IIA.

Details of construction of retaining plates at foot end of calf plethysmograph. (i) Inner retaining plate; (ii) outer retaining plate viewed from plethysmograph aspect; (iii) section through centre of plates viewed from side.

Catheter lubricant is smeared on the distal surface of the cuff and the foot is inserted into the plethysmograph, with the heel and sole resting on the rubber pads provided. The cuff is kept in place by the retaining plates and winged nuts. The temperature of the air in the plethysmograph is adjusted to the required level by circulating water through the outer jacket.

The instrument is calibrated and tested for leaks by the injection of a measured volume of fluid (usually five and 10 millilitres) into the calibrating mechanism, while an assistant operates the camera. The fluid injected must be at the same temperature as the air in the plethysmograph, otherwise the latter is cooled or heated and a faulty calibration is obtained. A typical calibration curve is shown in Figure III.

The venous occlusion cuff is loosely applied to the limb as close as possible to the plethysmograph and held in position by a lightly applied crêpe bandage. Before each recording the tap of the T-connexion behind the manometer is momentarily opened to the external air and then closed; thus one ensures that the pressure inside the plethysmograph is atmospheric. Recordings are made by quickly opening the tap connecting the reservoir, containing air under a pressure of 70 millimetres of mercury, to the cuff for about six seconds, after which the cuff is deflated. Meanwhile an assistant operates the camera. A series of six recordings is made, several seconds being allowed between tracings so that the veins may collapse. The average blood flow calculated from these tracings is called the "resting blood flow".

In the case of calf plethysmography, the proximal retaining plate and sponge rubber cuff are first applied to the limb; then the cylindrical part of the plethysmograph, the distal sponge rubber cuff and the retaining plate are applied in turn. The lower half-plates are applied to fill up posterior prolongations of the apertures

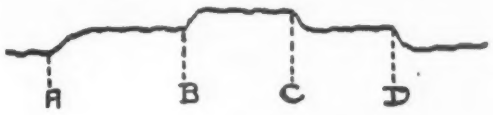

FIGURE III.

Calibration curve. At A and B, five millilitres of fluid were injected through the calibrating pipette, and at C and D five millilitres were withdrawn.

in the retaining plates. In addition to the venous occlusion cuff applied immediately proximal to the plethysmograph, an arterial occlusion cuff is applied immediately distal. During recording this cuff is kept inflated at a pressure above the systolic arterial blood pressure.

In cases of peripheral vascular disease, in order to determine how much the blood flow in the affected part can be increased, a reactive hyperæmia test is performed. In this, arterial occlusion is maintained by the application above the knee for ten minutes of a sphygmomanometer cuff, inflated to a pressure above the systolic blood pressure. The pressure in the cuff is then quickly released and blood-flow recordings are made by the method already described, at quarter-minute intervals for two minutes. The blood flow calculated from the steepest tracing so obtained is called the "maximal blood flow from reactive hyperæmia". (However, it should not be supposed that this is the maximal possible blood flow, as Scheinberg and others (1948) have shown, by means of a water plethysgraph, that the blood flow with the limb surrounded by water at 45° C. is much greater than that following ten minutes' arterial occlusion with the limb surrounded by water at 32° C.)

The volume of the limb enclosed in the plethysmograph is determined by water displacement, or in the case of the calf it may be calculated with sufficient accuracy from the length and mean circumference.

The method of obtaining measurements from the flow curves and of calculating the blood flow is best appreciated by reference to the example in Figure IV. It is to be noted that the first rapid rise of the curve following the venous occlusion is discarded, this being due to the forcing of fluid and tissue from beneath the cuff into the plethysmograph; it should also be observed that only that part of the flow curve before it begins to flatten out is used.

Possible Errors in Plethysmography.

Some Possible Errors in the Apparatus.

The plethysmograph must be sufficiently rigid not to be deformed by the small changes of pressure within it. As a possible weak part is the sponge rubber cuff surrounding the leg, it is supported by a backing of plaster of Paris; but we have shown that the omission of the latter causes no great error. The absence of any leaks and the use of properly fitting cuffs, which can make an air-tight seal of the limb in the plethysmograph without constricting the veins, are essential.

For accurate recording, the system must be able to respond with sufficient quickness to the changes in pressure in the plethysmograph. In our apparatus, in which air transmission to a Wigger's type of manometer as modified by Green (1947) is used, the frequency response is about 25 cycles per second (Figure V). As the frequency required for accurate recording need be only five times that of the changes one desires to measure, our apparatus should be adequate to record changes occurring over the period of one pulse wave (about half to one second).

Possible Errors in the Principle.

The validity of venous occlusion plethysmography depends on the assumptions that, after venous occlusion, blood continues to flow into the limb for a short time at the same rate as before, and that the increase in size of the limb is an index of this flow.

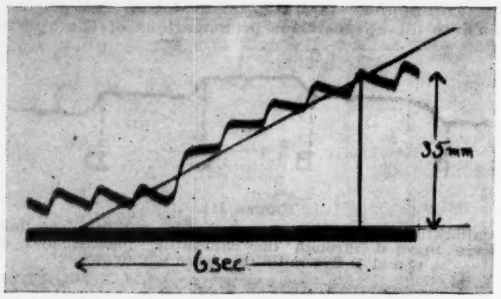

FIGURE IV.

A resting blood flow curve from foot showing lines used in calculating the blood flow. Rise of tracing, in millimetres per minute, $35 \times 10 = 350$ (a). Standardization factor (rise of tracing in millimetres per millilitre of fluid introduced into calibration balloon) from standardization curve, 3·7 (k). Volume of foot in units of 100 millilitres, 13·5 (v). Blood flow $= \frac{a}{kv} = \frac{350}{3{\cdot}7 \times 13{\cdot}5}$ = 7·0 millilitres per 100 millilitres per minute.

It may be asked: Does the application of the venous occlusion cuff in fact occlude all the veins, some of which accompany arteries deeply situated between the bones of the leg? The fact that the veins are, for practical purposes, occluded is evidenced by the fact that we have found that the same blood flows are recorded with different venous occlusion pressures varying from 50 to 80 millimetres of mercury. Also in our experiments the recorded blood flow was not increased by the substitution of a wider cuff for the one used.

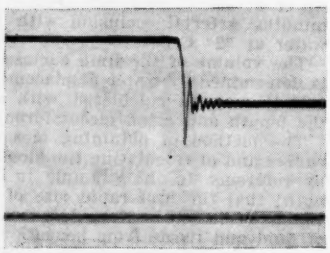

FIGURE V.

Frequency response curve. This was obtained by pulling out the stopper through which the calibrating pipette was inserted after injecting air into the plethysmograph. Frequency of the system recorded is about 25 cycles per second.

It may be asked whether the arterial inflow may not also be impeded by the application of venous occlusion. As the venous pressure is below the diastolic arterial pressure, the arteries will not be constricted by it. It may be suspected that the arterial inflow may be impeded secondarily to the occlusion of the veins. However, until they are at full bore the pressure in the veins is negligible and will offer no obstruction to the arterial inflow. In order to ensure that the veins are collapsed, the lower part of the limb is slightly elevated and the limb is inspected for the absence of venous congestion after the cuff is applied and before the limb is placed in the plethysmograph. If venous congestion is present the recordings are valueless. As was mentioned previously, blood flow is calculated only from the first part of the curve before it begins to "flatten out" as a result of venous congestion.

In the case of calf plethysmography it is assumed that all the blood entering the enclosed portion of the limb comes from the proximal arteries, and that none is returned from the more distal part of the limb. The fact that the pressure in the arterial occlusion cuff distal to the plethysmograph is above the systolic arterial blood pressure is certainly sufficient to cause collapse of any veins in the soft tissues. However, there is a possibility, if the arterial circulation is not occluded beyond the plethysmograph, that blood may be returned by emissary veins emerging from bone in the enclosed part of the limb. The fact that there is no gross error from this has been determined by noting the effect of varying the pressure in the arterial occlusion cuff on the recorded blood flow. Thus, in one subject we found that the recorded blood flow was the same when pressures in the arterial occlusion cuff of 280, 220 and 160 millimetres of mercury were used (all above the systolic arterial blood pressure in this case). If an error had been caused by blood returning by emissary veins from bone emptying into the enclosed part of the limb, this would be expected to be greatest when the lower pressures in the arterial occlusion cuff were used, as these would be less likely to occlude all the arteries completely.

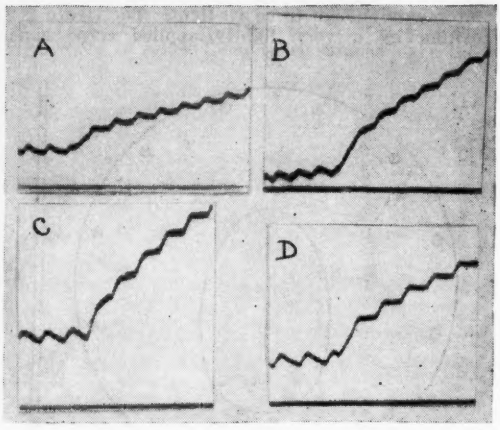

FIGURE VI.

Reactive hyperæmia. A., resting blood flow curve for foot; B., C., D., blood flow curves obtained one-quarter of a minute, three-quarters of a minute and eight minutes after release of arterial occlusion which had been maintained for ten minutes. It is to be noted that the reactive hyperæmia blood flow had not reached its maximum value in the first quarter of a minute after release of arterial occlusion.

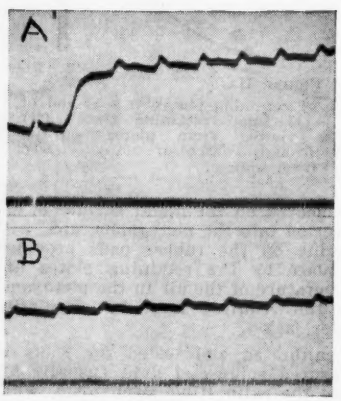

FIGURE VII.

Effect of position of venous occlusion cuff. Blood flow tracings obtained from calf with the venous occlusion cuff applied, A., immediately above the plethysmograph, and B., above the knee. The blood flow calculated from tracing B. is considerably less than that calculated from tracing A.

The validity of the reactive hyperæmia test may be questioned. That the increase in blood flow is a true reactive hyperæmia and not simply the result of the release of the arteries after occlusion is evidenced by the fact that the

maximum blood flow from this test does not occur immediately on release of the arteries, but often some forty-five seconds or more later (Figure VI), and that there is no such increase in blood flow if the occlusion is maintained for only a short time—for example, thirty seconds.

Possible Errors in the Method.

The necessity for avoiding venous congestion has already been stressed. Thus it is essential that no constriction be caused by the rubber sleeve, sponge rubber cuff or venous occlusion cuff before inflation, and it is advisable to have the distal end of the limb slightly elevated above the proximal end.

It is essential to avoid leaks, which are most likely to occur where the limb is sealed in the plethysmograph by the cuff and sleeve. Leaks are tested for by injecting fluid into the graduating balloon and noting whether the increase in pressure so produced is maintained.

The correct placing of the venous and arterial occlusion cuffs is essential. Thus it has been shown that a considerable under-estimate of the blood flow is made if the occlusion cuff is placed above instead of below the knee in calf plethysmography (Figure VII). It will, therefore, be readily appreciated that a correct estimation of the finger blood flow cannot be made by the use of a venous occlusion cuff at the wrist, as is done by some workers. An error in the opposite direction may be made in calf plethysmography if the arterial occlusion cuff is not placed immediately distal to the plethysmograph.

Some control of the room and plethysmograph temperatures is necessary. It is a well recognized fact that vessels dilate in response to heat (Lewis, 1927). However, in our experiments in which air plethysmography was used, the temperature of the air in the plethysmograph could be changed from 35° to 45° C. without detectable alteration of the calf blood flow. Even in the case of the foot, changing of the temperature of the air in the plethysmograph from 35° to 45° C. produced less increase in the blood flow than did immersion of another limb in hot water, and much less than the reactive hyperæmia test. These findings are in contrast to the sensitivity of blood flow to the temperature change in water plethysmography, presumably because heat is more readily transferred to the tissues from water than from air. By means of the apparatus described, it is possible to maintain the temperature of the air in the plethysmograph within a range of ± 0·5° C. Constancy of the room temperature is important and more difficult to obtain. However, it has been shown that small changes in the room temperature, as from 23° to 25° C., do not cause an appreciable change in the recorded blood flow.

Conclusion.

In conclusion, it is not claimed that plethysmography is a method of high accuracy; but it is believed that if the precautions mentioned are taken possible errors may be minimized, and that by this means valuable information may be obtained concerning the peripheral circulation.

Summary.

The principle of venous occlusion plethysmography is described. A short outline is given of the history of this procedure in research and clinical medicine.

It is held that the method has important applications.

A description of a method of plethysmography in which an air plethysmograph and optical recording system are used is described.

Possible errors in plethysmography are discussed.

Acknowledgements.

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THE EXTENDED RADICAL VULVECTOMY OF STANLEY WAY.

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SQUAMOUS CARCINOMA of an external body surface is essentially a disease of local proliferation and destruction, and of spread by lymphatic vessels to the regional lymph nodes and beyond. Theoretically the optimal treatment for cure of its lesions is free excision, widely skirting the growth superficially and deeply, and extirpation of the lymphatic vessels and the regional lymph nodes, advancing to the group of nodes higher than those likely to be involved.

In only one region of the body is this example of surgery able to be followed and that is the vulva. In other sites, such as the tongue, lip, face or cutaneous surfaces of the upper and lower limbs, the essential wide excision may be limited because of mutilating effects, and even if the regional lymph nodes are excised the intervening lymphatic vessels still remain.

Perhaps, if the lymphatic spread of squamous carcinoma is by lymphatic embolism and not permeation, the factor of preservation of the intervening lymphatic vessels may not be of such prime importance, but in radical cancer surgery completeness of excision is an objective for which one should strive.

Consequently in an area such as the vulva, which allows of the performance of the principles of radical surgery, this method should take pride of place in our selection, unless the operative risks are prohibitive or the results of cure from other procedures do not suffer in comparison.

Primary carcinoma of the vulva, up till comparatively recent years, although occurring infrequently, has always been a most forbidding lesion, because of the extremely

bad and discouraging results of treatment, whether by surgery, as in so-called radical vulvectomy with superficial groin-gland dissection, or by radiotherapy. In the last decade, however, a stimulating and enlightened outlook has developed, as the recently accepted treatment for this condition is now attended by five-year cure figures not bettered by any form of genital cancer in the female. This revolutionary welcome change has been made possible by the contributions of Taussig, Bassett, Stoeckel and Stanley Way, who may be regarded as surgical pioneers in this field.

Each of these contributors has added to the methods of treatment that should be employed now: Taussig by his courage in emboldening other surgeons to treat their patients more radically and by showing through his results the manifest advantages; Bassett by his extension of the lymph-node dissection above the inguinal ligament to extirpate the deep femoral node of Cloquet and by demonstrating the necessity and wisdom of dividing Poupart's ligaments; Stoeckel by his extraperitoneal approach to the external iliac glands; and Stanley Way by combining all the advantages of his predecessors and extending the radical nature of the operation by an entirely adequate excision of the vulval area, and by complete removal *en bloc* of potentially affected tissue, the intervening lymphatics and the lymph-node bearing area extending high enough to include the external iliac nodes.

The results that accrue from this extended radical vulvectomy of Way can now be seen to be worth while when one views them in comparison with other methods of treatment, of which radical vulvectomy (which, however, made possible closure of the raw area by suture), with dissection of the superficial inguinal and superficial femoral lymph nodes on both sides, gave the best figures. In a representative series of 53 patients treated by this method it was found that 56% died before the end of three years, 21% survived for the five-year period and only 5% were alive after ten years (Way, 1948).

Stanley Way, however, reported with his extended radical procedure an absolute three-year survival rate of 88% and a five-year cure rate (in a limited series of 12 cases) of 83%; Taussig's figures are comparable with a larger series of cases.

The salvage rate, therefore, in the extended radical operation, compared with the hitherto used so-called radical vulvectomy with bilateral superficial groin-gland dissection, is of such magnitude as to stifle criticism, and this with an operability rate of 85% (Way).

The surgical operation previously performed failed in three fundamental respects. Firstly, local recurrence was altogether too common and could be attributed to inadequate excision of the vulval area, as the excision which enables the edges to be approximated by primary suture is incomplete. Secondly, the lymph-node extirpation did not follow anatomical knowledge, as only the superficial or lower nodes were removed. Thirdly, the intervening tissue with the lymphatic vessels between the growth and nodes was not satisfactorily removed, and also anatomical exposure was unfavourably influenced by intact Poupart's ligaments.

In the light of Way's results, carcinoma of the vulva can be viewed in true perspective as being, next to uterine-body cancer, the least malignant type of growth in the female genitals, since approximately 50% of cases can be prevented (by simple excision of precancerous *leucoplakia vulvæ*) and over 60% of patients can be permanently cured.

This improvement in surgical results is especially welcome as treatment with radiotherapy has not merited any confidence. Any dosage sufficient to cause even a temporary retrogression of the tumour is very apt to produce burning, which in the vulval area is always extremely painful and slow to heal. There appears to be a hypersensitiveness of the vulval skin to such rays, and radionecrosis is a disappointing sequel.

The practically uniform failure of either X rays or radium to produce even a temporary alleviation of symptoms, appreciably permanent diminution in size of the tumour mass or arrest of the growth in lymph nodes suggests that radiotherapy should be relegated to a subsidiary place to surgery in treatment.

In this paper primary carcinoma is the only vulval lesion discussed, and Taussig, from the wealth of his experience, has classified these growths according to their site, which has an important bearing on their prognosis regarding lymphatic spread.

The anatomical forms are epidermal, clitoral, vestibular and glandular (Bartholin). The epidermal form is by far the most frequent and affects the labial, perineal and preputial skin; in most cases it springs from leucoplakic vulvitis affecting the sexual skin. Carcinoma of the clitoris (clitoral form) is a rare lesion and is commonly confused with the epidermal form when it affects the clitoral prepuce. Vestibular carcinoma may produce, from its extension from the vestibule, involvement of the urethra, or it may spread to invade the vaginal wall. Bartholin-gland cancer is a special rare type and may be adeno-carcinomatous or squamous in type depending on its origin from the gland or the duct (Taussig, 1941).

The location of the lesion has a bearing on the lymphatic spread of the malignant disease, and the lymph drainage of the vulva and the exact topography of the regional lymph nodes are essential features in treatment.

The lymphatic system of the vulva is a dense and freely communicating network on each side, and from the anatomical point of view a vulval cancer cannot be regarded as a unilateral lesion. Injection of the soft tissues of the labia with a dye (like trypan blue) will show ready transmission bilaterally to the regional lymph nodes, which can be divided into six main groups. The superficial inguinal nodes lie in the superficial fascia along the line of and slightly below Poupart's ligament; the superficial subinguinal or superficial femoral nodes are grouped around the great saphenous vein as it passes through the *fossa ovalis* to the femoral vein, and are divided into groups lying in association with the main high tributaries of the great saphenous vein. These two main groups of nodes are the superficial set and were the only lymph nodes excised before the extended radical operation was introduced. The deep set consist of the deep femoral nodes, which lie in the superior aspect of the femoral canal above the inguinal ligament, the most important and constant one being the gland of Cloquet; the deep inguinal nodes, an inconstant group lying in the inguinal canal and disposed around the extraperitoneal portion of the round ligament; and the external iliac nodes, which lie in three groups in relation to the external iliac vessels—lateral, anterior and medial. The medial group are the most important and are concerned with drainage from the vulval and vaginal zones; they are overhung by the external iliac vein. Lastly, the presymphyseal lymph nodes are small and lie in the lymphatic communications in the fatty tissue of the *mons veneris*.

The lymphatic spread, then, may be as follows: (*a*) from a growth of the epidermal form of *carcinoma vulvæ*, confined to the skin of the labia, perineum and clitoral prepuce, to the superficial inguinal and superficial femoral nodes, and later secondarily to the next chain of deep glands (deep femoral of Cloquet and medial external iliac) on one or both sides; (*b*) from a growth of the vestibular form involving the urethra or spilling over to the vaginal wall, or from a growth involving the body of the clitoris (clitoral form), a direct intrapelvic spread being likely involving the deep femoral, the medial external iliac (and very rarely the obturator and hypogastric) nodes, with the possibility that the superficial nodes may or may not be by-passed.

In regard to lymph-node involvement there are several conditions. (*a*) Contralateral spread is always likely, but particularly is this so with clitoral or fourchette growths. (*b*) The size of the primary growth does not run coincidently with the degree of node involvement. (*c*) No importance can be placed in the degree of palpability of the nodes, as impalpable superficial nodes may be involved, and palpable superficial nodes may not. (*d*) The superficial group of nodes may be by-passed under certain circumstances, and intrapelvic spread may occur primarily.

The essential features of the extended radical operation are based chiefly on the following principles: to overcome the vagaries of lymph-node involvement and to remove all nodes that could be affected; by a deep, wide and bilateral excision of the primary growth to prevent local recurrence; by removal of tissue in continuity and in one stage to remove the potentially affected intervening lymphatics from the growth to the superficial nodes.

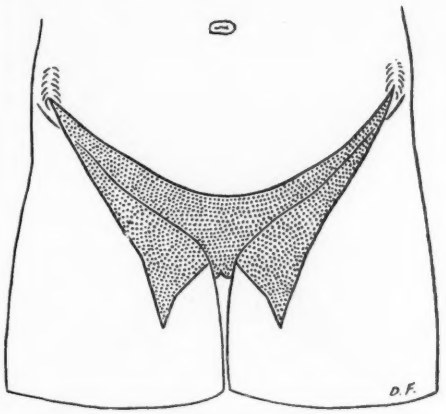

FIGURE I.

The area of tissue removed is extensive and comprises that mapped out by incisions joining the anterior superior iliac spines across the top of the mons, incisions on both sides passing from the anterior superior iliac spine downwards to a point below the *fossa ovalis* in the thigh, and from there a secondary incision marking out a small triangular area over the course of the saphenous vein in the upper part of the thigh (Figure I). The medial limb of this incision joins with the incision for excision of the vulval area, which continues from the groin excision down the inner side of the top of the thigh as far back as the ischio-rectal fossa and deep enough to expose the periosteum of the *symphysis pubis* (Figure V). The whole of this area of tissue, then, is finally removed in one piece; its depth in its upper part is to the external oblique aponeurosis and rectus sheath, and in the thigh to the fascial coverings of the upper part of the thigh musculature (Figure II).

The inguinal ligaments on both sides are divided, and the external iliac vessels are fully exposed extraperitoneally. The large vessels are stripped clear of loose areolar tissue and lymph nodes in continuity from below upwards from the femoral vessels just below the *fossa ovalis* to the external iliacs at the bifurcation (Figure IV). The great saphenous vein is ligated at its entrance to the femoral vein.

The operation is completed by closing the inguinal canal (previously opened to excise the extraperitoneal portion of the round ligament and deep inguinal nodes when present), and by closing the femoral canal by suturing the conjoined tendon and lateral part of the rectus sheath to the periosteum of the pubis. The inguinal ligaments are not sutured directly. The lateral incisions are sutured interruptedly, but the excised vulval area is left open (Figure V). The vulva is preferably excised by the diathermy knife and hæmostasis obtained mainly by electrocoagulation. Post-operative weeping from the raw surface is obviated by spraying this area with thrombin in saline, which forms a protective coagulum. Elevation of the level of the urethral meatus by means of lateral sutures and the insertion of an indwelling catheter (Foley type) are the final steps.

Occasionally the operation has to be modified to meet with the extension of the growth. If the urethra is encroached upon or frankly involved, it can be resected up to half its length without the occurrence later of incontinence of urine. If the anus is similarly involved, it should be excised and a colostomy performed at a later stage.

The operation is an extraperitoneal one, and the degree of shock is lessened thereby. The aproach is not attended by undue bleeding, and in fact there should be minimal blood loss. The length of the operation is an important factor in old women, and a period of less than two hours

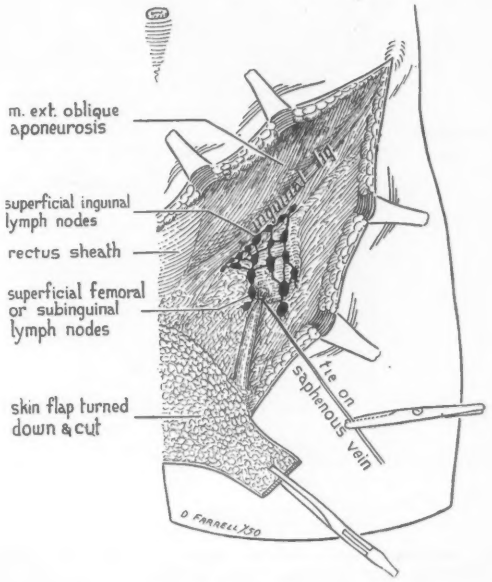
m. ext. oblique aponeurosis
superficial inguinal lymph nodes
rectus sheath
superficial femoral or subinguinal lymph nodes
skin flap turned down & cut
tie on saphenous vein
D. FARRELL X30

FIGURE II.

is necessary. Resuscitation measures are used during the operation, and blood transfusion administered at this stage to a large extent obviates primary or delayed shock and replaces protein.

The post-operative period is remarkable for the comfort of the patient and the absence of pain from the extensive wound. Early ambulation is advisable if the patient's general condition admits of it; with the catheter clipped, it is usual, particularly in the case of these aged women, for them to start walking on the fifth post-operative day. The lower limbs have to be bandaged to reduce lymph-œdema, which is always present and usually lasts for three months.

The age of the patient does not appear to be a bar to the successful performance of this operation, as the very elderly patient withstands the operation well. Careful post-operative supervision is necessary in regard to wound infection, electrolytic balance, protein replacement, pulmonary hypostasis, cardiac and circulatory derangement, and renal function. The intravenous administration of fluid has to be carefully controlled in old women; intragastric tubal administration of fluid and protein is much safer and is very effective in combating dehydration with its attendant oliguria and azotæmia.

The groin wounds can be expected to heal by first intention in seven to eight days, but primary healing of the vulval area within six weeks is not possible without skilful, energetic and vigilant nursing care. Skin grafting does not appear necessary and is inadvisable for the aged patient, as it adds a further raw surface and primary taking of the grafts in this area is unusual. A mild degree of wound sepsis is unavoidable, but is controlled by local and parenteral measures; bacteriological investigation should be used freely.

Dry methods of wound treatment appear to be more satisfactory for elderly women than the use of the saline bath; the infra-red lamp is of value, but should not be

used in association with sulphanilamide applied locally. *Tulle gras* is a most satisfactory dressing, but the type of local dressing has to be changed to conform with the condition of the wound.

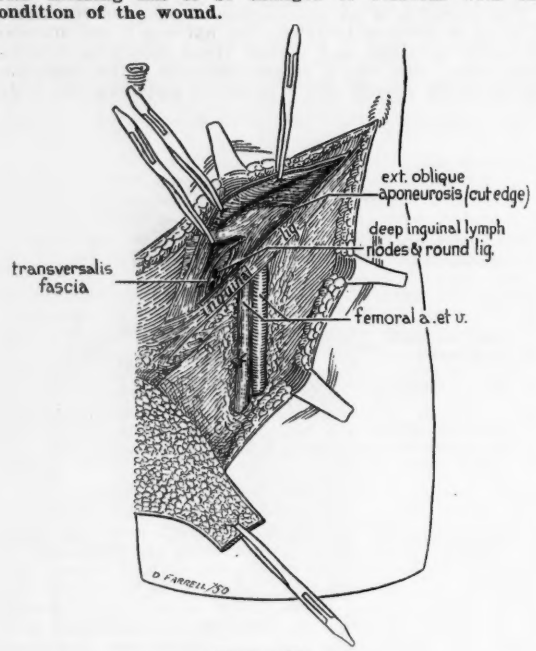

FIGURE III.

The ultimate, fully healed result of this operation is cosmetically satisfactory, not incapacitating, and fully functional, and the prognosis regarding cure of the malignancy is very good.

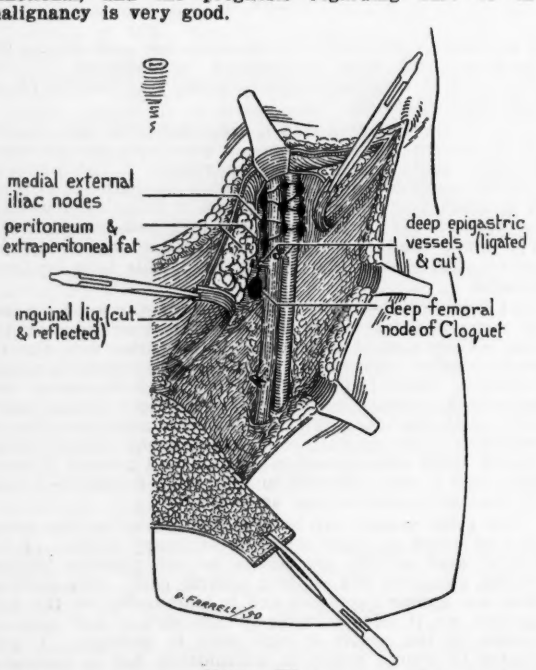
medial external iliac nodes
peritoneum & extra-peritoneal fat
deep epigastric vessels (ligated & cut)
inguinal lig. (cut & reflected)
deep femoral node of Cloquet
D. FARRELL '50

FIGURE IV.

Eight patients have been treated by this extended technique of Stanley Way since December, 1949, and their ages have been sixty-five, seventy-two, eighty-one, seventy-six, seventy-five, seventy, sixty-eight and fifty-three years. There has been no primary operative mortality, but one patient, aged eighty-one years, died three months after her discharge from hospital with a terminal pulmonary condition with hæmoptysis. Four of the patients can be

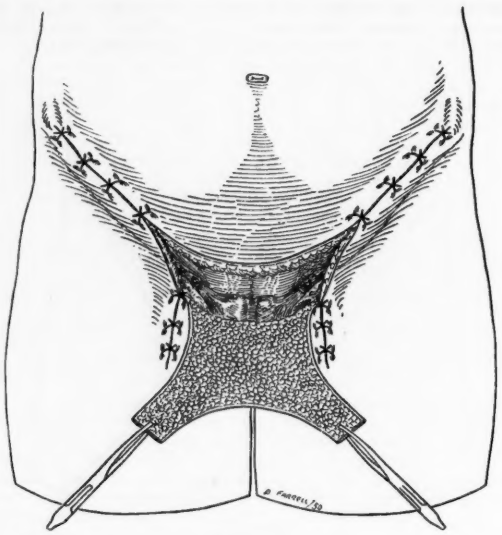

FIGURE V.

regarded as very advanced in the stage of continuous local pain, discharge and irritation. In five lesions on section involvement of the regional lymph nodes was found, and in three of these the upper set of nodes (the

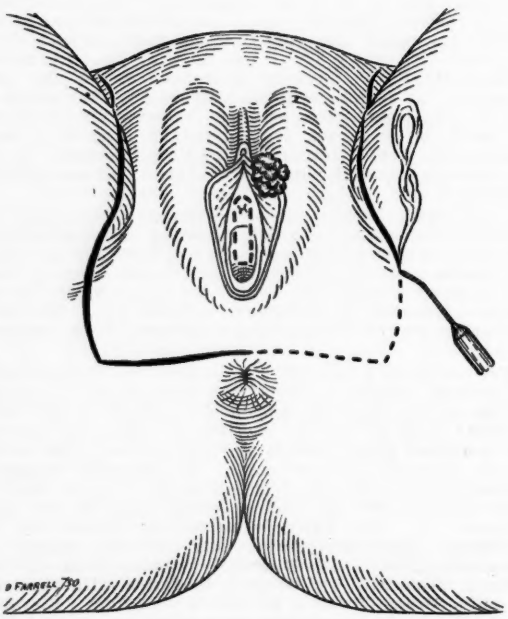

FIGURE VI.

deep femoral of Cloquet and the medial external iliac nodes) were involved. In one instance it was necessary to resect the lower half of the urethra to extirpate the growth adequately, and in another to excise the anus for

an extensive growth of the fourchette which was spilling over to the anal margin. In two instances the groin wounds did not heal by first intention. The average time of almost full healing to allow of the patient's safe discharge from hospital was six weeks. The average time for post-operative ambulation was the fifth day.

Conclusion.

An attempt is made to compare the manifest advantages of the extended radical vulvectomy (Stanley Way technique) with the previously used so-called radical vulvectomy and other methods of treatment of carcinoma of the vulva.

The potentiality of an operation that admits of a most radical surgical undertaking in the aged patient with a disproportionately minimal disturbance calls for greater efforts and cooperation to make the story of carcinoma of the vulva a safe one with a happy ending.

Acknowledgement.

Very sincere appreciation, thanks and full acknowledgement are made to Dr. Stanley Way of Newcastle-on-Tyne, England, for his kindness in demonstrating his operation and technique to me in July, 1949, and for his guidance and helpful criticism since that time by correspondence, and my gratitude is expressed to Dr. Clement Chapman, Dr. George Stening and Dr. Frederick Chenhall (senior honorary gynæcological surgeons, King George V Memorial Hospital, Sydney) for their helpful cooperation.

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RECURRENT ABDOMINAL PAIN IN CHILDHOOD.[1]

By E. S. STUCKEY,
Sydney.

The Problem.

MANY children are examined at our out-patient departments whose chief complaint is recurrent abdominal pain, and in whom little abnormality can be found clinically. This paper is an analysis of the records of 100 such patients who have been investigated and operated on with a view to discovering the part played in such cases by disease of the vermiform appendix. The cases presented, with few exceptions, have been referred from my own out-patient department with an adequate history, the results of necessary pre-operative tests, and thorough operation notes. In addition, an attempt has been made to obtain a histological report on the appendix removed, and to follow up the patient until cure or failure to cure is certain. The only basis used in selection of cases has been the sufficiency of data. I had hoped to present a much larger series of cases, but it is surprising and annoying to find how many otherwise suitable cases have had to be excluded because data were insufficient. None of these cases has been a definite case of acute appendicitis, however mild. Each has presented the problem: "Can I honestly recommend appendicectomy as a likely cure for this patient?"

[1] Read at a meeting of the Section of Pædiatrics, Australasian Medical Congress (British Medical Association), Seventh Session, Brisbane, May-June, 1950.

A few patients treated by other surgeons in the hospital have been included, and I should like to thank them for allowing me to use their cases in this study.

The Clinical Picture.

Every child complained of recurrent abdominal pain, usually central, but sometimes in the right iliac fossa or other area. Associated symptoms commonly admitted were nausea, listlessness and a sallow colour during attacks. The bowel habits may or may not be affected, and urinary symptoms are usually absent.

Only 58 of the cases were considered to have a sufficiently detailed history to be included in this analysis of symptoms and abnormalities (see Table I).

TABLE Ia.
Analysis of Symptoms in 58 Cases.

Symptoms or Abnormalities not Related to Attacks.	Number of Subjects.
Described as "highly strung" child ..	42
Tonsils and adenoids removed	36
Worms known to be present	9
Frequent coughs and colds	8
Previous pyelitis (once only)	7
Enuresis	6
Feeding problems in infancy	5

Attacks vary considerably in frequency, duration and severity, but it is usually possible to classify the "usual" attack in each case into a particular type. The types vary from the occurrence of short attacks almost daily

TABLE Ib.
Symptoms During Attacks.

Symptoms or Abnormalities.	Number of Subjects.	Symptoms or Abnormalities.	Number of Subjects.
Abdominal pain ..	58	Diarrhœa	13
Anorexia	55	Dysuria	12
Nausea	49	Desire to defæcate ..	6
Sallowness	43	Coryza	5
Listlessness	43	Bad breath	3
Feverishness	31	Nightmares	3
Vomiting	28	Other symptoms (one each)	9
Disturbed sleep ..	20		
Constipation	15		

to the occurrence of attacks lasting for several days at rather long intervals. Although the latter type of attack is more suggestive of appendicitis, analysis of the cases shows that no such inference can be drawn, and the appendix may be at fault in all the types studied.

Physical examination typically reveals very little abnormality. No masses are palpable except in a few cases in

TABLE Ic.
Details of Abdominal Pain.

Type of Pain.	Number of Cases.
Mainly epigastric	3
Mainly umbilical	31 } 58
Mainly right iliac	24
Central, *plus* right iliac ..	27
Radiating to right thigh ..	3
Partly left-sided	2
Related to exertion	24
Related to fatty foods ..	2
Related to other foods ..	3

which one fancies mesenteric glands are palpable, or in which fæces can be felt in the sigmoid colon. Tenderness is not pronounced but there is usually some slightly and consistently tender area on deep yet gentle palpation.

This requires a cooperative patient and usually several attendances before one can say that tenderness is consistently present. In my experience there is frequently some deep tenderness in the right iliac fossa at McBurney's point, but more often there is an area either in or deep to the right rectus muscle about one inch below the umbilicus, or even level with it, where tenderness is more definite, and there may be a tendency to guarding there. Sometimes there is a similar area in the left rectus, usually level with the umbilicus or slightly above it. Sometimes there is slight deep tenderness low down on both sides, just above the pubic arch, and this I believe is more likely when the appendix is medial or pelvic in position. Slight tenderness towards the right flank is possible when the appendix is paracaecal or retrocaecal. In spite of these remarks about tenderness, I should like to say that in most cases my resident medical officer's notes, on examination of a patient on admission to hospital, state that there is no tenderness in the belly. This emphasizes that the tenderness described is by no means like what one expects in a clear case of appendicitis.

TABLE Id.
Types of Attacks: Periodicity.

Type of Attack.	Number of Cases.
Type I: lasting up to one hour, occurring daily or almost daily	23
Type II: lasting up to several hours, occurring every week or two	27
Type III: lasting up to several hours, occurring at longer intervals	7
Type IV: lasting half a day to several days, occurring every few weeks	18
Type V: lasting half a day to several days, occurring at longer intervals	16
Type VI: Uncertain, or grossly irregular	9
Total	100

Nearly every patient has had a pre-operative urine examination and a blood count, and in suitable cases contrast X-ray films of the alimentary canal or renal tract have been taken. In some cases blood sedimentation rate estimations, chest skiagrams and Mantoux tests were thought advisable. No patient was submitted to operation until it was thought that other likely causes of pain had been excluded, and that attacks had recurred over a long

TABLE Ie.
End Results Compared with Type of Attacks.

End Results.	Type I.	Type II.	Type III.	Type IV.	Type V.	Type VI.
Cure (appendix abnormal), 44 cases	7	14	4	7	8	4
Cure (appendix normal or not examined), 33 cases	10	9	1	6	5	2
No cure (appendix abnormal in 6 cases), 9 cases	5	2	0	1	0	1
Uncertain (appendix abnormal 9 cases), 14 cases	1	2	2	4	3	2
Totals (100 cases)	23	27	7	18	16	9

enough period for one to feel certain that they were not likely to disappear spontaneously. A few patients were submitted to operation in the knowledge that they had other lesions—for example, recurrent pyelitis or tonsillitis—but in these cases it was believed that the appendix was probably also at fault, usually on the strength of suggestive findings on X-ray examination with the use of barium. When such a finding suggested a diseased appendix, it was found in all cases either that the appendix was diseased or that the patient was cured by its removal, or both.

Differential Diagnosis.

The possible causes of recurrent attacks of abdominal pain are numerous, but adequate pre-operative investigation will narrow the likely causes down to a few, and

TABLE IIa.
Position of Appendix at Operation.

Position of Appendix.	Percentage of Cases.
Anterior: running forwards among loops of ileum	13
Medial: running medially, deep to mesentery of small bowel	20
Pelvic: running downwards over the brim of the pelvis	17
Subcaecal: tucked up beneath the free part of the caecum (partial mesoappendix)	23
Retrocaecal: running up behind the caecum towards the kidney (no mesoappendix)	26
Paracolic: lying in whole or in part in the right paracolic gutter (partial mesoappendix)	1

findings at operation will exclude some of these—for example, Meckel's diverticulitis, malrotation of the gut, obstruction from bands, internal hernia and regional ileitis. When the appendix removed is not obviously

TABLE IIb.
Naked-eye Appearances at Operation.[1]

Appearance in Appendix.	Number of Subjects.	Comment
Innocent	31	15 had microscopic pathological appearances
Inflamed	46	33 had microscopic pathological appearances
Thickened	19	14 had microscopic pathological appearances
Adhesions *et cetera* present	17	11 had microscopic pathological appearances
Concretions present	6	3 had microscopic pathological appearances
Not noted	3	2 had microscopic pathological appearances

[1] Note that some cases presented more than one abnormality.

diseased, one may still be in doubt about the diagnosis until such time as a pathological report on the organ, or a follow-up of the patient, or both, help one in arriving at a decision. Conditions which are difficult to exclude, even after operation, are as follows: (i) colic due to dietetic or allergic causes; (ii) colic due to constipation or laxatives; (iii) colic due to oxyuris infestation; (iv) the mesenteric lymphadenitis syndrome; (v) recurrent

TABLE IIc.
Lymph Node Enlargement in Relation to Appendiceal Abnormality.

Microscopic Pathological Appearances.	Lymph Nodes.[1]					Total.
	N	+	++	+++	(?)	
Acute changes only	7	6	5	1	2	21
Acute *plus* chronic changes	2	1	2	0	0	5
Chronic changes only	4	6	10	2	3	25
Normal or near normal	13	9	9	3	0	34
Not examined	5	5	2	1	2	15
Totals	31	26	28	7	8	100

[1] "N", no enlargement; "+", doubtful enlargement; "++", enlargement in ileo-caecal area only; "+++", enlargement all the way along the mesentery, sometimes without much enlargement in the ileo-caecal angle; "?", no notes made at operation.

upper respiratory tract infection with abdominal pain; (vi) undiscovered renal abnormalities; (vii) testicular or ovarian pain; (viii) migraine or cyclic vomiting attacks.

Findings at Operation.

A Meckel's diverticulum was discovered, and removed, on three occasions. It was looked for in all cases. However, it was not thought to be the cause of symptoms

in any case, as the three diverticula removed were essentially normal and were in each case associated with a diseased appendix. No case of regional ileitis occurred in the series; such patients are usually admitted to hospital with the diagnosis of acute appendicitis. One patient had a partial chronic intestinal obstruction due to adhesions after a previous bout of appendicitis (unrecognized). No other gross abnormalities were discovered at operation. In almost all cases the position of the appendix was noted at operation, and any naked-eye evidence of recent or past attacks of appendicitis was noted. I was surprised to note the frequency of positions in which the appendix was relatively inaccessible to the examining fingers and to the sensitive anterior parietal peritoneum. Possibly that is why most of these patients showed so few physical signs. In this connexion it is necessary to remark that unless the surgeon makes an effort to note the position of the appendix prior to delivery of the caecum into the wound, he will in most cases have very little idea what position it occupied. The only other observation consistently made at operation was the state of the mesenteric lymph-nodes. They have been graded as follows: (*a*) no enlargement, 31%; (*b*) doubtful enlargement, 27%; (*c*) enlargement in ileo-caecal area only, 28%; (*d*) enlargement all the way up along the mesentery, sometimes without much enlargement in the ileo-caecal angle, 7%; (*e*) no notes made at operation, 7%.

TABLE IID.

Lymph Node Enlargement in Relation to Rate of Cure.

End Results (Rate of Cure).	Lymph Nodes.[1]	
	"N", or "+", or "?".	"++" or "+++".
Cured, 60 cases	42	18
Partial cure, 17 cases	6	11
Uncertain, 14 cases	10	4
No cure, 9 cases	7	2
Totals	65	35

[1] "N", no enlargement; "+", doubtful enlargement; "++", enlargement in ileo-caecal area only; "+++", enlargement all the way along the mesentery, sometimes without much enlargement in the ileo-caecal angle; "?", no notes made at operation.

TABLE IIIA.

Summary of Histological Findings.

Histological Findings.	Number of Cases.	
No report available	15	(appendix not examined)
Normal appendix	22 (25·9%)	of appendices examined
Minor changes only	12 (14·1%)	
Acute inflammation	21 (24·7%)	
Acute *plus* chronic changes	5 (5·9%)	
Subacute inflammation	9 (10·6%)	
Chronic lymphoid appendix	8 (9·4%)	
Fibrosis of appendix	8 (9·4%)	

Analysis shows that in all these groups histological examination of the appendix frequently revealed pathological changes, but that the percentage of complete cures was less when the glands were definitely enlarged.

TABLE IIIB.

Summary of Minor Abnormalities.

Changes Noted.	Alone. (Number of Cases.)	With Other Abnormality. (Number of Cases.)
Ecchymosis of mucosa	7	7
Eosinophilia of mucosa	3	5
Œdema of appendix	1 (12)	(?)
Concretions in lumen	1	6
Oxyuris in lumen	13	22

It is advisable at this stage to discuss the syndrome known as non-specific mesenteric lymphadenitis, which may be acute, subacute or chronic. It is held by most authors that appendicectomy fails to cure this condition and that it is a common cause of recurrent abdominal pain. My impressions are as follows.

1. There is such a specific syndrome, but it is far from common and should be diagnosed only when mesenteric lymph nodes are evenly and noticeably enlarged, preferably when all mesenteric glands are affected, not merely the ileo-caecal group.

2. If it is assumed that such enlargements arise from an infection in the lymphoid tissues of the ileum, perhaps a virus infection, the appendix may also be affected as part of this process, and may in such cases present pathological changes when examined histologically.

3. Appendicectomy in such cases may produce partial relief of symptoms, and since diagnosis is never certain in this syndrome, appendicectomy should be performed.

4. In many cases mild to moderate enlargement of the ileo-caecal group of mesenteric glands is directly due to repeated mild attacks of appendicitis, in the same way as

TABLE IVA.

End Result in Relation to Pathological Report.

Pathological Findings.	Cure.	Partial Cure.	Uncertain Result.	Failure.
No examination made, 15 cases	12	1	1	1
Normal appendix, 22 cases	15	3	2	2
Minor changes, 12 cases	5	2	5	0
Acute inflammation, 21 cases	15	3	1	2
Acute *plus* chronic inflammation, 5 cases	2	1	2	0
Subacute inflammation, 9 cases	4	3	1	1
Chronic lymphoid appendicitis, 8 cases	2	3	2	1
Fibrosis of appendix, 8 cases	5	1	0	2
Totals, 100 cases	60	17	14	9

TABLE IVB.

Probable Cause of Failure.

Case Number.	Pathological Findings.	Lymph Glands.[1]	Comments.
I	Acute inflammation only.	N.	Aged 11 years, menstruates, pain possibly ovarian.
II	Chronic lymphoid appendicitis.	N.	Associated with frequent upper respiratory tract infection.
III	Fibrosis of appendix.	(?)	Associated with constipation and frequency of micturition.
IV	Acute inflammation only.	N.	Probably renal; also "worms" present.
V	Subacute inflammation.	(?)	Irregular attacks with diarrhœa.
VI	Appendix not examined.	N.	Probably pyelitis (recurrent).
VII	Normal appendix.	N.	Aged 11 years, possibly ovarian, puberty present.
VIII	Normal appendix.	++	Associated with recurrent upper respiratory tract infection.
IX	Fibrosis of appendix.	++	Operation for obstruction due to adhesions some months later.

[1] "N", no enlargement; "+", doubtful enlargement; "++", enlargement in ileo-caecal area only; "+++", enlargement all the way along the mesentery, sometimes without much enlargement in the ileo-caecal angle; "?", no notes made at operation.

enlargement of cervical lymph nodes is an indication of previous attacks of tonsillitis. In such cases appendicectomy may be expected to cure the symptoms.

FIGURE I.
Normal appendix (× 100). Note well-defined lymph follicle, deep and clear crypts and open-textured stroma between crypts.

5. The dividing line between the cases due primarily to appendicitis and those due to inflamed intestinal lymphoid tissue cannot with certainty be drawn either preoperatively or at operation, or even on the result of histological examination of the appendix.

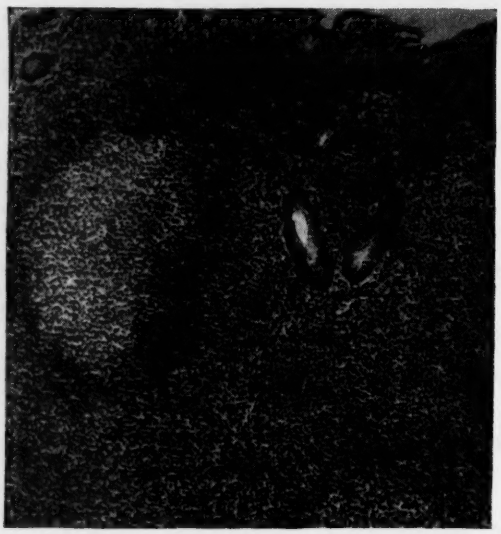

FIGURE II.
Chronic lymphoid changes (× 100). Note lymph follicle spilling over into stroma. The crypts are partly obliterated and pushed aside by lymphoid tissue, and the whole mucosal layer is thickened.

Histological Findings.

Most of the appendices were examined by our pathologist, Dr. Douglas Reye, and I should like to thank him for the trouble he has taken and the interest he has shown. The only cases included in which such examinations have not been made are those in which cure is known to have followed operation, or in which abnormality visible to the naked eye was present.

The abnormalities found varied from nil to chronic fibrosis of the appendix; they are listed in Tables IIIA and IIIB.

It is notable that in 22 cases the report was "normal appendix", and in a further 12 cases minor changes only

FIGURE III.
Chronic fibrosis in submucous layer (× 100). Note the fibrous tissue and the scarcity of lymphoid tissue. There is no active inflammation.

were detected. But the removal of such essentially normal organs frequently resulted in complete cure of the patient. I think the explanation is that the appendix is an organ which has considerable powers of recovery from repeated mild attacks of inflammation, so that when removed in the interval between attacks it need not show any evidence of past attacks. It is also notable that only a few appendices show histological changes which justify a diagnosis of subacute or chronic appendicitis, and it must be recognized always that when clinicians use such terms they are not speaking scientifically but are using the term in an everyday sense. It would be better to speak of "recurrent mild acute appendicitis", and if an effort is made to keep hospital records scientific there should be a classification such as "recurrent appendicitis—appendix normal when removed".

Chronic fibrosis may perhaps be accepted as due to past attacks of inflammation. It is not so easy to decide about the cases classified as chronic lymphoid appendicitis. We recognize the relative lymphoid hypertrophy which occurs in childhood, and in the only cases listed as "chronic lymphoid appendicitis" the appendix was considered by Dr. Reye to be abnormal. The histological appearances are shown in Figures I to VI.

Brief reference must also be made to oxyuris infestation. It was found in only 33 of 85 cases in which the appendix was examined histologically, and it was not a prominent feature in the history. Cases in which oxyuris was

present in the appendiceal lumen included the following: normal or almost normal appendix, 13; acute or subacute inflammation, 10; acute *plus* chronic changes, five; chronic changes only, five. There is insufficient evidence to incriminate this worm as a cause of mild appendicitis or of recurrent pain. Mucosal eosinophilia, when present, was not always associated with oxyuris infestation, nor did eosinophilia found at the blood count bear any constant relationship to the presence of oxyuris.

FIGURE IV.
Chronic fibrosis of deeper layers (× 100). From the same section as Figure III. Fibrosis down to muscular layer, *plus* some fatty deposits (abnormal at this age).

The possibility of true "allergic" appendicitis in cases in which eosinophlia was found in the mucosa must be borne in mind; it occurred as the only histological abnormality in three cases and in association with other changes in six cases. There were, however, only two cases in which mucosal eosinophilia was present but oxyuris infestation was absent.

Rate of Cure.

End results have been carefully collected. The following *questionnaire* was sent to all parents and 84 replies were received.

1. Has the operation cured the attacks which used to occur?.....
2. Does the child still have attacks of abdominal pain?.....
3. How often do such attacks occur?.....
4. How long does each attack last?.....
5. What other symptoms occur with each attack? Nausea: vomiting: fever: diarrhœa: constipation: headache: listlessness: sallow colour: bad breath: head colds: sore throat: difficulty or frequency in passing urine. (Underline the ones which occur.)
6. What other illnesses has the child had since operation?.....

As many patients as possible had already been followed up after operation until cure was certain or the patient ceased to bother returning. The period since operation in many cases exceeds two years, and in some cases three years have elapsed. The results have been listed as follows: complete cure, 60 cases; partial cure, 17; uncertain result, 14; failure, nine. The partial cures refer to cases in which symptoms have been markedly relieved but not abolished after operation, and the uncertain cures refer to cases in which the follow-up notes are inadequate (10), or

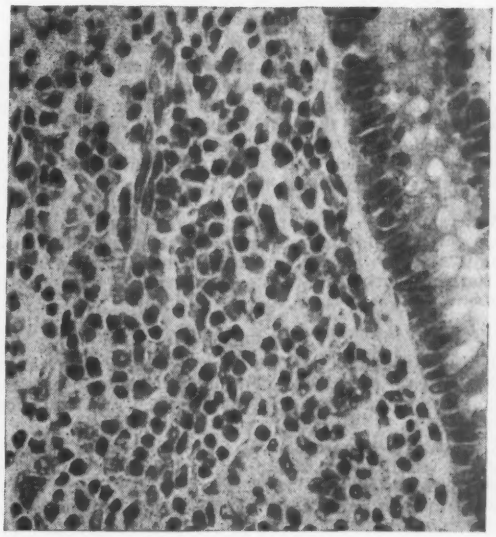

FIGURE V.
Subacute inflammation (× 450). The stroma between two crypts is densely infiltrated by plasma cells. Few polymorphonuclear cells are present.

in which a sufficient period has not yet elapsed for the result to be certain (four).

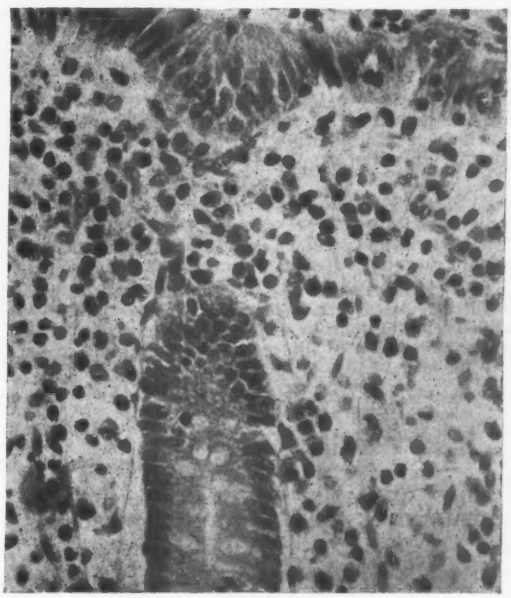

FIGURE VI.
Mild, diffuse, acute inflammation (× 450). The stroma cells are separated by œdema, and numerous polymorphonuclear cells are scattered through the subserous layer, spilling onto the surface and also migrating from blood capillaries (at left, lower corner).

When we compare the end results with the pathological report, we find that failure to cure and partial cure occurred in cases in which there was evidence of acute,

subacute or chronic inflammation, as well as in cases in which the appendix was classified as "normal" or "near normal". It is difficult to explain why this is so. Perhaps some patients had inflamed lymphoid tissue in the lower part of the ileum as well as in the appendix.

If we compare the rate of cure with the state of the mesenteric lymph nodes we find a similar inconsistency. Failure to cure was associated with normal lymph nodes more often than with much enlargement. Partial cure, however, although occurring in all types of case, was more frequent in cases in which glandular enlargement was present. However, complete cure followed in four of the seven cases in which generalized enlargement of all mesenteric glands was present—a surprising result. (See Table IID.)

Analysis of the nine failures is of interest. Some of these patients did not bother to attend for proper follow-up examination, but an attempt to hazard a guess as to the reason for continued attacks of abdominal pain has been made in all these cases.

Conclusions.

1. The appendix must be suspected as the cause of symptoms in all cases of mild or moderate recurrent abdominal pain, irrespective of periodicity or duration of attacks.

2. Physical examination in such cases gives essentially negative results, and diagnosis is based on a process of exclusion. However, a "suggestive" X-ray report after an opaque meal is usually correct. Slight deep tenderness is commonly present.

3. The appendix is frequently found to be in a position where it is not readily accessible to the examining fingers or to the parietal peritoneum.

4. Enlarged mesenteric glands are more likely to be a sign of recurrent appendicitis than of the syndrome known as non-specific mesenteric lymphadenitis.

5. There is probably such a disease as non-specific mesenteric-lymphadenitis, but it is not common, and it is not possible to distinguish it from recurrent appendicitis prior to operation.

6. Removal of the appendix, even in cases in which considerable enlargement of mesenteric glands is present, will frequently cure the patient's symptoms.

7. The removal of an apparently normal appendix, even one which is histologically normal when removed, will frequently cure the symptoms and need not throw doubt on a diagnosis of "recurrent appendicitis—appendix normal when removed".

8. Pathologically the condition of subacute or chronic appendicitis is not common, and such terms as used by clinicians are not scientific, except occasionally.

9. Oxyuris infestation has no constant relationship with appendiceal disease, nor is eosinophilia in the bloodstream or in the mucosa of the appendix an indication of oxyuris infestation in all cases. In some such cases the condition may be due to food allergy.

Reports of Cases.

FOLIC ACID AS AN ADJUVANT TO SULPHAPYRIDINE IN DERMATITIS HERPETIFORMIS.

By JAMES MOLESWORTH,
Sydney.

THE following short reports are those of two of a small series of eight cases.

Case I.

Mr. A.B., aged forty years, was first diagnosed fifteen years ago as suffering from *dermatitis herpetiformis*. Three years ago he was first treated at a public hospital with sulphapyridine, which was given in doses of six tablets (3·0 grammes) daily. However, many groups of small vesicles continued to appear, and itching persisted in many of the areas. After nine months he suffered from diarrhœa and nausea, and I understand that at that time a blood count revealed that he had less than 2000 leucocytes per cubic millimetre, of which less than 40% were neutrophile cells. Since that date he had been unable to take, without recurrence of nausea and diarrhœa, more than four tablets (2·0 grammes) daily. Six months ago he consulted me. When first examined he showed the typical symmetrical itching groups of vesicles on the feet, legs, thighs, buttocks, and front and back of the chest and arms. The areas on healing left typical brown patchy pigmentation. Attempts to control his intolerance with alkalis, vitamin *B* group injections *et cetera*, failed completely. At this stage he was started on two tablets (1·0 gramme) daily of sulphapyridine, together with one tablet (5·0 milligrammes) three times a day of folic acid. Within a week it was noticeable that no fresh vesicles or bullæ were appearing. After three weeks there remained only light brown pigmentation in the areas previously affected, and he states that he was, for the first time since the onset of the disease, completely free of itching. This state of affairs has persisted ever since, despite the reduction of the folic acid dosage to two tablets (10 milligrammes) daily, the sulphapyridine dosage being maintained at 0·5 gramme three times daily.

Case II.

Mr. G.R., aged fifty-five years, has been a patient of my father for twenty-five years, having been diagnosed by him as suffering from *dermatitis herpetiformis* in 1925. His condition was only partially controlled by large doses (up to 18 minims per day) of *Liquor Arsenicalis*. By 1945 his hands and feet were covered with arsenical keratoses, and in 1947 he became intolerant of arsenic, and the practitioner in whose care he was informed me that sulphapyridine had produced on three successive occasions a neutropenia sufficiently alarming to warrant a blood transfusion. The repeated exhibition of sulphapyridine and arsenic was necessitated by the recurrent acute exacerbations of his *dermatitis herpetiformis* which had endangered his life. Two years ago he was given a trial of treatment with one gramme of sulphapyridine daily, together with 20 milligrammes of folic acid, and later his condition became stabilized on two tablets (10 milligrammes) of folic acid and two tablets of sulphapyridine daily. He has remained well since this date.

Comment.

Early investigations of the literature with regard to the interrelation between sulphapyridine and folic acid reveal some interesting and perhaps significant relationships. Firstly, folic acid deficiency can be artificially created in some experimental animals by the administration of large doses of sulphapyridine. Secondly, folic acid is produced in and absorbed by the bowel by the activity of certain bacteria normally living in the bowel. Thirdly, the metabolism in the body of folic acid, para-aminobenzoic acid, the sulphonamides and aminopterin are known to be closely associated with one another (Kornberg *et alii*, 1945; Spicer *et alii*, 1947; Kornberg *et alii*, 1943).

It is tentatively suggested that further investigation may well show that folic acid deficiency is an important factor in the causation of toxic symptoms by the sulphonamide group of drugs, and this aspect is being investigated.

It is quite obvious that these remissions could be purely coincidental, and that in a disease notorious for spontaneous exacerbation and remission it would be unwise to draw any firm conclusion from these few cases. However, it is suggested that where danger to the white cells from sulphapyridine exists, and where doses result in toxic symptoms of any sort, folic acid in doses of from 10 to 20 milligrammes per day may enable adequate dosage to be maintained.

Acknowledgement.

My thanks are due to Dr. C. Wallace Ross for his assistance in the search of the literature.

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Daft, F. S. (1947), "Folic Acid: Physiological Aspects", *Annals of the New York Academy of Science*, Volume XLVIII, page 299.

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Spicer, S. S., Daft, F. S., Sebrell, W. H., and Ashburn, L. L. (1942), "Prevention and Treatment of Agranulocytosis and Leukopenia in Rats Given Sulfanilylguanidine or Succinyl Sulfathiazole in Purified Diets", *Public Health Reports*, Volume LVII, page 1559.

Reviews.

DISEASES OF THE FOOT.

THE second edition of "Diseases of the Foot" by Emil D. W. Hauser, of Chicago, enhances the reputation of this monograph.[1] The author covers the subject very widely. The early chapters on anatomy, physiology and the common static deformities provide a useful introduction to the more specialized conditions which are described later. Special chapters are also devoted to fractures, congenital abnormalities, and circulatory disturbances. The author is able to write with a simplicity and assurance which enliven the text and maintain interest in what is often regarded as a dull part of the body. Treatment for each condition is given in considerable detail and in many cases alternative methods are described.

The illustrations are well chosen and all, including several in colour, are beautifully reproduced. The production maintains the high standard associated with W. B. Saunders. This book can be confidently recommended, not only to the orthopædic specialist, but also to the physician and general practitioner. Many foot disorders are medical as much as surgical problems, and often the foot condition is merely a local manifestation of a generalized disease.

CLINICAL NUTRITION.

KNOWLEDGE regarding the nutritional aspects of metabolism in man is now a vast and specialized field. The Food and Nutrition Board of the National Research Council (United States of America) has entrusted the task of assembling an authoritative text on human nutrition to three distinguished physicians, Norman Jolliffe, Frederick Tisdall and Paul Cannon.[2] The chapters have been written by 36 American and Canadian authorities in various aspects of the subject.

"Clinical Nutrition" is divided into three parts: diagnosis (which includes the pathogenesis of deficiency diseases); the nutrient elements; and prevention and therapy. An appendix is included containing much useful tabular material such as food value tables and ideal weights for American men and women.

The clinical signs (including X-ray appearances) associated with deficiency diseases have been grouped, described and illustrated (mostly in colour) in a very readable and useful manner. Suitable emphasis is placed on the fact that many of the clinical signs in cases of deficiency diseases are non-specific and must be evaluated in the light of the total history. We learn that weight scales are still of paramount importance in evaluating nutritional status; that the diagnosis of nutritional deficiencies is at a stage comparable with clinical medicine before use of X rays; and that chemical methods of determining nutriture have been devised, but that individual variations are such that most of these methods are worthless except when applied to group surveys analysed by statistical procedures.

Part Two, dealing with the nutrient elements, perhaps does not contain a great deal of information which is not available from other texts, but the subject matter is comprehensive and very well presented.

A feature of Part Three which deals with prevention and treatment is the excellent chapter on obesity contributed by L. H. Newbergh. The space devoted to this subject is amply justified by the importance of obesity among the nutritive diseases, and also by the misconceptions about it which often exist in the literature and in the minds of practitioners. Impressive evidence is included to convince all that obesity is the result of an excessive calorie intake and can be remedied by a suitable restrictive diet. A very interesting selection of case histories emphasizes how frequently "excessive eating is an expression of mood . . . a behaviouristic response to a person's environment". The book includes a useful presentation of the dietotherapy of systemic diseases including such recent methods as intravenous therapy with amino acids, and the Kempner rice diet for the treatment of hypertension—which is still to be regarded as experimental.

The text very effectively and authoritatively covers all aspects of clinical nutrition including its physiological basis, and the prevention, diagnosis and treatment of disordered nutrition. It is lucid, is printed in the best style of modern medical publications, and will prove invaluable to all who have a vital interest in the application of present-day knowledge and nutrition.

ENDOCRINOLOGY.

"SYNOPSIS OF ENDOCRINOLOGY", by Dr. Ross Wilson Hawker, is published in Brisbane.[1] As the author states in the preface, the aim is to give the student a brief survey of the endocrine system. It is in three parts. In the first part, which comprises four-fifths of the book, the history, anatomy, histology, embryology and physiology of each endocrine gland are treated with the thoroughness for which the foreword by Dr. H. G. McQuiggan, senior lecturer in physiology at the University of Sydney, prepares us. Glandular interrelationship is not neglected. The arrangement is clear and concise. The historical section is good, and adds to the interest. An ample bibliography follows the account of each gland. Mandl's pioneer surgical attack on a parathyreoid tumour has, however, been overlooked. It was obviously impossible to consider the ramifications of Selye's adaptation syndrome. Moreover, what is up to date here today might not be tomorrow.

Two smaller parts entitled "Integration and Adaptation" and "Introduction to Clinical Endocrinology" complete the book. The latter is mainly a recapitulation of the first part and, by some, might be thought redundant. Endocrine therapy is not discussed, but its basis is given.

It is pleasing to note the appearance of Australian books such as this. It is all the more our duty to point out certain blemishes if such productions are to reach international standard.

The paper is not good, its colour varying in different parts. Numbering and lettering of headings in the second part need correction. The punctuation in the last paragraph of page 70 is wrong. The proof-reading has not been above reproach and some of the references are defective or incorrect. It is a pity that the necessary accents are not used with foreign words. Careful attention to such details, however, would enhance the reputation of Australian works abroad. We nevertheless recommend this synopsis. It is packed with information, and is a very good introduction to works more concerned with treatment. Royalties are directed to "The Robin May Memorial Fund".

THE PHYSIOLOGIST.

"RECENT ADVANCES IN THE PHYSIOLOGY OF VISION", by Hamilton Hartridge,[2] is deceptive in its compact size, for within its modest-seeming covers is an abstruse analysis of at least 90% of the controversial and problematical matters confronting those who would essay to understand

[1] "Diseases of the Foot", by Emil D. W. Hauser, M.S., M.D.; Second Edition; 1950. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 9" x 6", pp. 432, with 195 illustrations. Price: 66s. 6d.

[2] "Clinical Nutrition", edited by Norman Joliffe, M.D., F. F. Tisdall, M.D., and Paul R. Cannon, M.D.; 1950. New York and London: Paul B. Hoeber, Incorporated. 9¼" x 6", pp. 940, with 127 illustrations, some of them coloured. Price: $12.00.

[1] "Synopsis of Endocrinology", by Ross Wilson Hawker, M.B., B.S. (Sydney); 1950. Brisbane: William Brooks and Company (Queensland) Proprietary, Limited. 8½" x 5½", pp. 230.

[2] "Recent Advances in the Physiology of Vision", by Hamilton Hartridge, M.A., M.D., Sc.D., M.R.C.P., F.R.S.; 1950. London: J. and A. Churchill, Limited. 8" x 5½", pp. 420, with 236 illustrations. Price: 25s.

and apply the laws of physics, chemistry and biology to the elucidation of the wonderful faculty of sight.

It is hard to determine whether this book should be reviewed by a physiologist or an ophthalmologist, for some of the discussions are wholly physiological, but the clinician will find in it plenty of stimulating interest for him. Those looking for dogmatic solutions will be disappointed, for conclusions are few, but anyone interested in something more than their daily clinical bread will be more than rewarded by a perusal of the book.

There are eight main headings: the basic properties of vision, the perception of shape and size, investigations of retinal function, the perception of colour, theories of vision, neurology of vision, properties of the structures of the eye and the appreciation of light and colour. These main headings are divided into seventy subsections, compact with statistical theorems and analyses, and the whole may seem to the practical man more academic than real, but of such is the kingdom of science.

The author concludes with a plea for further research into the essential nature of the visual receptors and their modes of stimulation.

THE PRINCIPLES OF ANATOMY.

THE third edition of A. A. Abbie's book maintains the aim and standard of the last edition, but a few sections have been expanded and largely rewritten.[1] This applies particularly to the sections on genetics and the problems of postnatal growth and bodily differentiation. The main aim of this work is to serve as an introduction to the study of man as a biological problem in relation to his environment, and so appropriate emphasis is given to the relation of function to structure. Mention is made of the newer work on the relation of molecular structure to gross structure and function, and of the recent news on nucleo-protein particles. Attention is again drawn to the chapter on the history of anatomy and the appendices which appeared in the second edition and provide useful information including a glossary of terms. The book maintains its usefulness as a valuable addition to the library of the student, providing as it does an excellent approach to the study of human anatomy. The figures are numerous and for the most part are simple and graphic, emphasizing essentials rather than details, and on the whole are very useful adjuncts to the text.

APPLIED PHYSIOLOGY.

THE fifth edition of Best and Taylor's "Physiological Basis of Medical Practice" has grown by about 150 pages and about 100 new illustrations have been added.[2] New material on pteroylglutamic acid and vitamin B_{12} has been included. A short discussion on "immersion foot" and frostbite has been introduced, and the section on shock has been expanded. There are brief references to noradrenaline and cortisone, and additions to the section on the physiology of the retina. The more recent information on the physiology of the frontal lobes is discussed, but other sources cover this subject much more satisfactorily. No mention is made of the work of Magoun and his colleagues on the functions of the reticulospinal system. The section on electrocardiography needed more drastic revision than it received. There is no mention of unipolar leads, and no mention of the controversy on the genesis of the electrocardiogram, a matter which is primarily within the realm of physiology at the present time.

An unexpected statement in the preface is that authorship responsibility has been indicated by initials at the beginning of each section. Inspection of the various sections reveals that in a book of 81 chapters, Professor N. B. Taylor has been responsible for writing all except four chapters and part of a fifth. To keep abreast of such a wide field of physiology and to integrate the multitude of subjects into an up-to-date book is a tremendous undertaking. The author upon whom most of this responsibility has devolved must be congratulated for the very great success that has attended his efforts. At the same time, it is difficult to avoid suggesting that unless an alternative method of revision can be found, this book will lose some of its popularity.

[1] "The Principles of Anatomy: An Introduction to Human Biology", by A. A. Abbie, M.D., B.S. (Syd.), D.Sc. (Syd. and Adel.), Ph.D. (Lond.); Third (Revised) Edition; 1950. Sydney, London, Angus and Robertson. 8½" × 5½", pp. 312, with many illustrations. Price: 25s.

[2] "The Physiological Basis of Medical Practice: A Text in Applied Physiology", by Charles Herbert Best, C.B.E., M.A., M.D., D.Sc. (London), F.R.S., F.R.C.P. (Canada), and Norman Burke Taylor, V.D., M.D., F.R.S. (Canada), F.R.C.S. (Edinburgh), F.R.C.P. (Canada), M.R.C.S. (England), L.R.C.P. (London); Fifth Edition; 1950. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 10" × 7", pp. 1330, with 601 illustrations. Price: £5 18s. 3d.

A POCKET OBSTETRICS.

THE second edition of "A Pocket Obstetrics" by Arthur C. Bell appears four years after the first.[1] The scope and size of the work remain unaltered, but changes have been made to bring it into line with some recent trends in obstetric practice. The book is intended to be a help to midwives and general practitioners and to students for revision. Hence a better description of the management of normal and of trial labour would be helpful. It is surprising that there is no reference to the importance of the regular weighing of ante-natal patients; and the advocacy of a low protein diet in toxæmia is not in accord with most modern teaching. In spite of these objections the book succeeds in giving a concise and clear outline of obstetrics.

CHANGE OF LIFE.

"MEDICA", the author of "Change of Life",[2] is herself a grandmother, as well as a medical practitioner of twenty-five years' standing. She has written it as much to dispel many of the fallacies handed down from generation to generation amongst women as to the evils which befall them during and after the menopause, as to provide positive evidence of the changes which occur, especially in the personality of the patient. After giving statistical tables of the incidence of the more important symptoms, she explains that most of the evils feared never really materialize, and briefly touches upon the psychological trends, such as masochistic tendencies, against which the middle-aged woman has to guard herself. One may question the wisdom of the inclusion by name, in the chapter headed "Useful Medicaments", of thyreoid extract and œstrogen on account of the tendency of the public at large to take such things without prior medical investigation and advice. With this exception the book is sound and can do nothing but good.

HUMAN EMBRYOLOGY.

DR. S. R. NAIR, Chief of the Department of Embryology, Topiwala National Medical College, Bombay, has recently published a small volume on human embryology designed for medical students.[3] He gives a straigntforward account of human development, illustrating his text mostly by simple line drawings and diagrams. Such photographs as are employed suffer because they are not reproduced on special paper. Students will find the simple text, which is clearly printed, easy to follow and will appreciate the tables of developmental defects at the end of each section. There are an adequate bibliography and index. The matter of the text does not call for particular comment apart from the fact that there is little evidence of any dynamic outlook on the factors involved in development. Chromosomes and heredity are almst completely ignored, and there is no mention of such conceptions as growth gradients and organizers. The most that can be said is that the book is simple and completely orthodox. Even in these times the price seems high.

[1] "A Pocket Obstetrics", by Arthur C. H. Bell, M.B., B.S., F.R.C.S., F.R.C.O.G., Hon. M.M.S.A.; Second Edition; 1950. London: J. and A. Churchill, Limited. 7¼" × 4¾", pp. 164, with 14 illustrations. Price: 7s. 6d.

[2] "Change of Life: Facts and Fallacies of Middle Age", by "Medica"; 1948. London: Delisle. 8¼" × 5½", pp. 84. Price: 7s. 6d.

[3] "Human Embryology for Medical Students", by Dr. S. R. Nair; 1950. Bombay: The Popular Book Depot. 8¼" × 5¼", pp. 416, with 241 illustrations. Price: £2 2s.

The Medical Journal of Australia

SATURDAY, DECEMBER 2, 1950.

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SPAS AND HEALTH RESORTS.

THAT mineral springs have a curative action on human ills is a belief which goes back far in antiquity. Archæologists have shown by the types of pottery, jewellery and weapons that "taking the waters" was a practice pursued before history could be written. Perhaps the Romans were the greatest organizers of the cult as the remains of characteristic masonry can be found in so many localities from Somerset in England to the valley of the Danube. The large number of such remains attests the addiction of the Romans to the use of mineral waters both ablutionary and therapeutic. Philologists explain many place-names as indicative of the appreciation and employment of mineralized water, for example, the root Hal in Central Europe denotes, we are informed, the presence of salt. This confidence in the efficacy of naturally occurring springs has lasted until our own day, though the revolution in thought following the publication of Darwin's "Origin of Species" just ninety-one years ago did much to lessen the established belief. For centuries no one thought of challenging the doctrine that thermal, sulphur, chalybeate and other waters had been placed there by a beneficent providence for the express purpose of curing or alleviating diseased states. When, in the first World War, the supply of Hunyadi Janos was cut off, earnest attempts were made in English-speaking countries, and probably many others, to reproduce exactly the composition of this aperient saline. Though we now regard mineral springs as a geological phenomenon or even freak, having nothing whatsoever to do with human needs, yet the tradition of specific efficacy survives. In general the more repellent the water, the greater has been the faith in its curative properties. This attitude has largely arisen through what in formal logic is called the fallacy of the undistributed middle—medicines are nasty in taste, this water is nasty in taste, and therefore it is probably a medicine. Hence huge hydropathic establishments were erected around springs of maladorous or bitter water each with excellent hotel accommodation and imposing a ritual with a certain amount of restraint upon its votaries whose improvement in health, when it occurred, was attributed to the water and not to the betterment in sleeping hours and the avoidance of excess in food and alcohol. More and more commercialized did the vogue become until almost any departure from the proper standard of potable water was hailed as a pretext for a "hydro" with highly developed advertising and expert salesmanship. If in addition to stinking or otherwise unpalatable fluid, there was found an abundance of hot or tepid mud close to the surface or lazily emitted from vents, the success of the district was ensured. Not even excessive and obvious business exploitation reduced the local inhabitants to scepticism, as, for example, when truck loads of synthetic chemicals were openly imported by the management of a well-known Czechoslovakian well to meet the situation caused by the demand for the bottled salt being greater than the supply.

Sustained efforts are now being made to revive the heyday of spas in Central Europe which once attracted wealth from many lands. There has recently been circulated in Australia a brochure sounding the praises of Piestany in Czechoslovakia; here are hot sulphur waters and above all copious sulphuretted mud which can, so it is alleged, cure an amazing number of maladies including iritis and flat foot. There are parks, swimming pools, a theatre, concert room, sports grounds of all sorts, suggesting rather a luxurious American country club than a place for the sick. British resorts have not been far behind in the exploitation of what Nature has provided in the matter of aberrant springs. An English antiquarian bookseller recently published a catalogue entitled "Medical Books with a Section on the Spas of Europe". Bath, of course, also Cheltenham, Malvern, Llandrindod and a number of places with names unfamiliar today, are given favourable notice. At a later date Harrogate and Leamington came into prominence and were duly lauded, not without abundant medical testimony. "New Australians" with medical degrees have commented on the absence of organized hydrology in the Commonwealth and some of these have offered their services. We doubt whether there will be a welcome given to such suggestions. A distinguished Australian professor of chemistry extolled the Hepburn Springs some seventy miles from Melbourne largely on account of the radioactivity present. Just why radioactive substances in solution should be curative was not stated. Another distinguished Australian, this time a member of the medical profession, wrote of the virtues of lithium water; whether lithium was actually present we may leave to those interested in the discussion, but though lithium citrate once had a vogue in gout and rheumatism, its use has greatly declined. At one time "lithia water" was a popular effervescent table drink, but the amount of lithium salt fell to vanishing point and the fluid became simply carbonated water, the so-called "soda water" of today. Australia has certainly an abundance of artesian bore water, often highly mineralized, to the annoyance of pastoralists and graziers. At Moree, for example, the water emerges at a temperature of 114° F. and is strongly alkaline with sodium bicarbonate predominating. Though it is useless for stock, no doubt remarkable cures can be claimed to follow drinking or immersion. Mittagong in the Camden Hills has a chalybeate water containing ferrous carbonate, but just what superiority this possesses over a Blaud pill is not stated. Muccadilla in Queensland has a hot bore water with some radioactivity, whilst

Helidon, forty miles inland from Brisbane, can offer a water which is both alkaline and chalybeate. In addition to these the number of bores must be legion which throw up a mineralized stream, whilst in summer many permanent creeks, in some cases following destruction of trees on catchment slopes, become so charged with dissolved salts that though sheep may not object, horses and cattle do. All of these could be exploited in mid-European fashion if the profession in Australia would tolerate such a procedure, but most probably it would not.

When we come to health resorts we are on much surer ground. Inhabitants of countries with cold, raw winters may for the preservation of health find it advisable, if they can afford it, to spend part of the year in a more favourable climate. A once well-known consultant physician in London brought economic satisfaction to Madeira by sending his pulmonary patients there. Many British people who have spent the best part of their lives in the tropics dare not, on retirement, go back to England and face its gloom and penetrating cold, especially when the east wind blows in winter. When one is asked which Australian localities can be labelled health resorts one must think a little before venturing on a reply. In fact the greater part of the Commonwealth may be regarded as a huge health resort. One day the remarkable, indeed unique, immunity of Australian tropics from serious tropic diseases will be recognized throughout the world and a considerable fraction of the country could easily become a sanatorium for white people suffering from rheumatic and pulmonary complaints. Extratropical Australia has been likened to California except that the counterpart to the Mohave Desert is inconveniently large; yet the portions which are suitable for residence are immensely greater than California and an approximate racial purity can be found which is by no means apparent in the Golden State. From the standpoint alone of health Australia, tropical and extratropical, can look forward to a rich future with ever-increasing certitude.

Current Comment.

ACUTE INFECTIOUS LYMPHOCYTOSIS.

THERE still seems to be room for further study of the infectious fevers. One reason for this is the fluctuating clinical picture in many infections, which present differing signs in separate epidemics, and often fail to produce signs rather rashly described as pathognomonic. Infectious mononucleosis is a disease which is often overlooked, especially if it occurs in surroundings where blood examinations are not readily made, or are not considered necessary. It is known to simulate a variety of other conditions, infectious or otherwise, but since 1941 another apparently distinct type of infection associated with a distinctive blood picture has been added to the list of imitators. This is the disease known as acute infectious lymphocytosis, to which attention was drawn by C. H. Smith in 1941, and which has been further studied by him and other observers since. John B. Moyer and George S. Fisher have published a study of five siblings who simultaneously presented signs corresponding with the description given by other writers on this disease, which appears to constitute a clinical and pathological entity.[1] The five children ranged in age from two and a quarter to ten years; they all had a mildly febrile illness, the temperature being raised for a week to ten days. All the children had diarrhœa, and one had signs of bronchitis; there was slight inflammation of the pharynx in three. The most striking sign common to all was a high lymphocyte count in the blood, but of equal importance was the fact that no enlargement of the spleen was detected, nor was any enlargement of the lymph glands present. The lymphocytes ranged in number per cubic millimetre from 22,000 to 79,000, and all but one of the patients had a relative and absolute eosinophilia. A leucopenia was observed in one case after the initial leucocytosis. The eosinophilia lasted for several months, but the increase in the lymphocytes lasted only for a few weeks at the most. Examination of the stools failed to reveal any pathogenic organism, and the diarrhœa soon disappeared. This description tallies with that given by others as distinctive of acute infectious lymphocytosis. The possibility of infectious mononucleosis at once is suggested in these obviously infectious illnesses, but a study of the blood morphology and immunology apparently disposes of this. Moyer and Fisher found that none of their patients had heterophile antibodies in their blood in a titre regarded as significant. This finding agrees with the experience of others, who have found that changes of titre may occur, but that these are not of the degree which is characteristic of infectious mononucleosis, and would appear to belong to the non-specific group of blood agglutination change familiar in other infections. More important still, abnormal lymphocytes were not found in the blood of these children. The lymphocytes were of the small mature type, not in the least resembling the mononuclear cell usually thought to be characteristic of mononucleosis of the infectious kind. These authors quote from 27 references to the literature, from which a consistent clinical picture and characteristic hæmatological findings have been built up. This condition should be looked for more frequently. In the past a high lymphocytosis has not infrequently caused anxiety, especially if it has been observed after the height of a febrile disturbance has passed, for the thought of leuchæmia has at once arisen in the mind of the physician. However, the anginose and the glandular types of mononucleosis are now well recognized, though the more indefinite type which may simulate a continued fever may cause confusion. Perhaps hidden away amongst various varieties of lymphocytic disease there are more cases of infectious lymphocytosis than are suspected, and if the blood morphology is studied carefully mistakes should not occur. It may be that unexplained eosinophilia occurring after a febrile episode may be due to the same cause. Moyer and Fisher, in issuing a warning against a precipitate diagnosis of leuchæmia, suggest that it would be wise for every patient suspected of suffering from one of the leuchæmias to be submitted to thorough study before any form of therapy is begun.

[1] *Blood*, July, 1950.

THE CARE OF THE DEAF.

IN his presidential address to the Section of Oto-Rhino-Laryngology at the Australasian Medical Congress (British Medical Association) in Brisbane earlier this year, G. C. Halliday discussed the problems associated with the care of the deaf in Australia. He brought into the light some of the defects in the present state of affairs and made practical and constructive suggestions for improvement. His recommendations, which may be found in more detail in the account of the congress proceedings (see THE MEDICAL JOURNAL OF AUSTRALIA, July 22, 1950, page 137), included the following: firstly, that the responsibility for the education of the deaf child should be on the community; secondly, that centres should be set up for the training of teachers and associate workers; thirdly, that hearing centres should be established in the large teaching hospitals; finally, that a consultative body should be established with committees in each State to coordinate the activities of the various agencies concerned in the care of the deaf. It is to be hoped that these recommendations are not going to be forgotten. The discussion that followed Halliday's address indicated that a certain amount was being done, but not sufficient and not always along the most desirable lines. Reference was made to one developing rehabilitation service that was "complete and

extensive", but entirely devoid of any medical direction. Comment on this state of affairs would be superfluous, but it should arouse the appropriate people to activity. One aspect of the subject that perhaps warrants more emphasis is the plight of the deaf adult. Much is being done or attempted for the deaf child, and no difficulty is usually experienced in arousing appropriate sympathy in either the public or the medical profession. The adult is more neglected, and not the least unfortunate is the private patient with nerve deafness.

This point has been recently taken up by an American otologist, L. E. Morrissett,[1] whose views bear careful thought. He has found that patients sometimes appear to show transient clinical improvement after a variety of forms of treatment; but when the period of observation and follow up has been adequate, not a single patient with nerve deafness has shown any significant sustained improvement. Aural rehabilitation appears to Morrissett to provide the only salvation for the nerve-deaf adult; the objective is to restore the patient to economic usefulness and to a normal social life. It is the responsibility of otologists, he contends, to move to bring about the provision of aural rehabilitation services for the deafened. In the United States there is a limited provision of this service in Veterans Administration hospitals and occasionally in public hospitals, but rarely in private hospitals. Services should include complete medical and otological study, audiometric and auricular-ability tests, psychological study, provision of a hearing aid, instruction in lip-reading, auditory training, voice training and speech correction, and vocational guidance. The practicability of such a programme in private otological practice is governed largely by economic factors, since much equipment, adequate space, and skilled personnel are needed. The average patient probably will be unable to pay for this treatment. The answer, according to Morrissett, is in the provision of mass facilities, either in community hospitals or through organizations of otologists in a form of group practice for this particular purpose. He holds that it should be the business of the otologist to supervise the selection and fitting of the appropriate hearing aid, and this can more reasonably be done in an aural rehabilitation centre. In his opinion systematic training in the use of hearing aids is an essential part of an aural rehabilitation programme. Considerable improvement in word comprehension is evident after a period of instruction. Combined training in the use of a hearing aid and in lip-reading is a practical phase of Morrissett's programme, for it has been conclusively shown that the test scores are more than doubled when the two are appropriately combined. For the purpose of the study and follow-up of each patient direct speech-hearing testing, with the use of controlled word tests, can be undertaken through an organized centre. Such estimations as the "social adequacy index of hearing" can be applied in each case for the evaluation of a hearing aid and of rehabilitation progress, a standard being thus provided for comparison of results achieved by various methods. The most important point, which is sometimes lost sight of at present, is that the patient's whole training and readjustment should be the responsibility of the otologist; or at least he should supervise it. It is to be hoped that the otologists will pursue with vigour the lead given them in Brisbane by Halliday.

[1] *Archives of Otolaryngology*, January, 1950.

THE INFLUENCE OF DIGITALIS ON COAGULATION OF THE BLOOD.

DIGITALIS is surely one of the most interesting of essential drugs. Not only has the use of the simple galenical preparations of foxglove and its modern refinements been of outstanding value to sufferers from various types of cardiac failure, but its study has been very rewarding in shedding light on several aspects of disordered metabolism. Over twenty years ago observations were made on the effect of strophanthin on the coagulation time in animals, and this has been followed since by the work of numerous investigators on the effect exerted by digitalis on the blood coagulation time. Both experimental animals and human subjects have been studied, but unanimity has not been reached, for one group of workers concludes that the drug accelerates clotting, and another group has been unable to verify this finding. George C. Sutton has published some fresh studies on this subject, and has based his work on the recent refinements in measurement of the coagulation time.[1] He points out that observations on the effect of different surfaces on clotting of blood have led to developments in the laboratory procedures, and that the use of heparin in particular has conferred greater accuracy in the determination of prothrombin, and in the measurement of small changes in the rate of clotting of blood or plasma. Therefore he first set out to examine the reliability of the Lee-White test, and adopted a standard procedure. His controls were adults, who were apparently in good health; he divided them into two chief groups. The first comprised sixty persons, for whom coagulation determinations were carried out simultaneously on the right and the left arms on two separate days, approximately a week apart; the other group included one hundred for whom a single test was performed. Single samples of blood of a small group of thirteen individuals were examined on from four to ten random occasions. The three test-tube method employed gave very similar mean times in all groups, approximately 10·4 minutes, with a range of eight to nine minutes and a standard deviation of two minutes. The coagulation times were then estimated in two groups of patients with established cardiac disease. The first group included sixty persons receiving therapeutic doses of digitalis with satisfactory results; the other group of ten persons was of particular interest as the patients were at the time of examination exhibiting signs of frank digitalis intoxication. Some estimations were also carried out under special circumstances, namely, after heparin was added *in vitro*, and when "Lucite" (methyl methacrylate) tubes were used instead of glass. In general it was found that there was no substantial difference between the various groups, regardless of the procedure employed. Estimation of the heparin tolerance curve failed to reveal any difference between persons who were receiving digitalis and those who were not. Obviously it was of interest to find out whether the state of the function of the liver had any substantial effect on the coagulation time. The coagulation time of fourteen individuals was estimated before and after the establishment of cardiac compensation, particularly to see if any difference could also be related to the liver function as revealed by the bromsulphthalein test. There was a slight lengthening of the clotting time after compensation was achieved, but it was not significant. Sutton concludes that the Lee-White test gave consistent results in all instances. He points out that the large standard deviation, which has been noted above, must be borne in mind when the results of work in this field are being assessed. The experimental error is considerable, and individual variation is great, and Sutton states that the coagulation time must vary by at least twice the standard deviation, two minutes, before the reading can be considered abnormal. As has been already mentioned, this work does not support the occurrence of alteration in the blood coagulation time, prothrombin time or bromsulphthalein retention of persons receiving digitalis, either before or after the establishment of compensation of the function of the heart.

It is relevant to point out that the bromsulphthalein test is only one of a large series of liver function tests. In the same journal L. Felder, A. Mund and J. G. Parker present a statistical analysis of ten liver function tests in a series of 135 patients with chronic cardiac failure. They find, as others have found, that since the liver has many functions, full experimental evaluation of these demands many tests and much study. However, they could find no definite pathognomonic pattern of impaired liver function in patients with long-standing congestive cardiac failure. It may be noted that they paid attention to the general state of nutrition of their patients in assessing the results. But without attempting to correlate blood coagulation with hepatic function in Sutton's series, we can find his work of interest in the story of digitalis and its powers.

[1] *Circulation*, August, 1950.

Abstracts from Medical Literature.

PÆDIATRICS.

Electroencephalography in Measles Encephalitis.

HORACE L. HODES AND SAMUEL LIVINGSTON (*The Journal of Pediatrics*, May, 1950) report the electroencephalographic findings in eight patients suffering from measles encephalitis. In all eight, the pattern was abnormal soon after the onset of encephalitis, slow high-voltage waves appearing. In a group of controls with uncomplicated measles the electroencephalographic pattern remained normal. In seven of the patients the electroencephalographic pattern became normal with clinical recovery. In the eighth patient no improvement occurred in clinical or electroencephalographic pattern.

A New Sulphonamide.

J. A. BIGLER AND O. THOMAS (*American Journal of Diseases of Children*, May, 1950) report the use of a new sulphonamide "Gantrisin". Its advantages are low toxicity and a high degree of solubility with no crystalliation in the urine in therapeutic dosage. Given to 71 children and infants with infection, it gave results comparable to those of other sulphonamides that the authors have used in like infections. Administration of alkalis did not seem to be necessary and reactions did not occur. The authors found neither crystalluria nor red blood cells in the urine.

Anticonvulsant Drugs.

JOHN A. ABBOTT AND ROBERT S. SCHWAB (*The New England Journal of Medicine*, June 15, 1950) discuss the toxic effects of the newer antiepileptic drugs. They state that "Dilantin" may cause nausea, vomiting, and occasionally diarrhœa, but these effects are lessened by giving the drug after meals and with plenty of water. Ataxia results readily from overdosage, with diplopia and hypertrophy of gums occasionally. Skin rashes occur. *Erythema multiforme* often occurs ten days or so after treatment with the drug is started, and if the drug is temporarily omitted, the rash does not recur on its being recommenced. Occasionally a morbilliform or purpuric rash or exfoliative dermatitis occurs. "Tridione" and "Paradione" may cause photophobia, gastric distress, nervousness, behaviour difficulties, dizziness or double vision. More serious effects on the blood and the skin may occur. There is no effect on the blood of 80% of patients, or so slight an effect that the number of neutrophile leucocytes remains above 3000 per cubic millimetre. In about 20% a controlled neutropenia occurs, the number of neutrophile cells falling below 3000 per cubic millimetre, but not low enough for dangerous clinical symptoms to occur. In an occasional case the blood count gradually falls to a dangerous level, the neutrophile cells first and then all formed elements of the blood. There is generally a preceding period of a few months of minor toxic symptoms and suspiciously low neutrophile cell count, and then suddenly a severe and fulminating illness occurs, with bleeding from the nose, skin, alimentary tract, kidney or uterus, uncontrolled infections, fatigue, dyspnœa and palpitation. Recovery may occur with transfusions, but death is likely. "Tridione" and "Paradione" may also cause rashes, erythematous, morbilliform, acneiform, urticarial, and occasionally exfoliative dermatitis. In one case corneal erosion and blindness occurred as well. The final serious toxic effect is the occasional development of nephritis of the nephrotic type; the patient improves on withdrawal of the drug. "Mesantoin" can cause blood changes and exfoliative dermatitis similar to those caused by "Tridione". "Phenurone" may cause personality changes, especially excitement and talkativeness, skin rashes, albuminuria and occasionally hepatitis. The authors emphasize the point that the cheaper and safer drugs, such as phenobarbital and "Dilantin", should be used first for any patient. If response is inadequate and the patient is reliable and accessible for dose control, the potentially dangerous drugs can be used. Their administration should be started in small doses, increasing as necessary. The blood and urine should be examined after one, three and five weeks, then each month for a year, and after that each three to four months.

Congenital Anomalies of the Œsophagus.

WILLIAM E. LADD (*Pediatrics*, July, 1950) discusses the diagnosis and treatment of congenital anomalies of the œsophagus. He states that early diagnosis is imperative, for infants tolerate major operations much better in the first two or three days of life than at the end of a week. This applies particularly to œsophageal atresia, for aspiration pneumonia is likely to occur and worsen the prognosis daily. An understanding of the embryology of the œsophagus is helpful. The trachea and œsophagus start as one tube and become separated by the ingrowth of muscle and connective tissue. An arrest of this process leaves the two tubes connected, with resultant tracheo-œsophageal fistula. Transverse pinching-off may cause a blind pouch or stricture of the œsophagus. During development the lumen of the œsophagus becomes obliterated by epithelial tissue. Failure to recanalize can cause the œsophagus to remain a solid cord or cause a stricture or obstruction by a velum. Duplication of the œsophagus may result from aberrations of canalization or separation from the trachea. The earliest symptom is usually an excess of saliva in the infant's mouth, accumulating because it cannot be swallowed. The chest may contain evidence of atelectasis. The abdomen may become tympanitic, if there is a connexion of the lower end of the œsophagus to the trachea, or remain flat and non-resonant, if no such connexion exists. The first fluid taken by mouth is promptly vomited. No further delay should take place. A soft rubber catheter should be passed, and if it meets obstruction about 10 to 12 centimetres from the lips, the diagnosis is confirmed. It is useful to run in about one millilitre of lipiodol to attempt to outline the type of obstruction and determine the presence or absence of a tracheo-œsophageal fistula. Under no circumstances must barium be used, for if it enters the lung it will cause pneumonia. If atresia is present the infant is placed in a slight Trendelenburg position and the pharynx aspirated constantly. If necessary a small blood transfusion is given. Operation is undertaken nowadays by direct end-to-end anastomosis of the œsophagus, if possible, with obliteration of the tracheal fistula, maintenance of the baby on parenteral fluid administration for a day or two, and then gastrostomy. Oral feeding is commenced about the tenth day. If end-to-end anastomosis is not possible, the older operation of multiple stages is carried out, the upper end of the œsophagus being brought out over the clavicle and anastomosed to a loop of jejunum that is brought up between the skin and the bony cage of the chest. For congenital strictures retrograde bouginage through a gastrostomy opening is recommended as the choice of several methods of treatment.

Neurological Sequelæ of Rh Sensitization.

P. R. EVANS AND P. E. POLANI (*The Quarterly Journal of Medicine*, April, 1950) report 16 cases of neurological sequelæ of severe neonatal jaundice, with serological evidence of Rh isoimmunization. They also analyse the findings in 63 cases from the literature and state that these are in general in close accordance with their own. The main features of the disease consist of a usually severe neonatal illness with jaundice, opisthotonus and muscular twitchings. This is followed by a latent period of a few weeks' or months' duration. Later, stiffness or hypotonia, and retardation, may be noticed. Of the older patients, over 80% have athetosis, chorea, or choreoathetosis. Mental defect is often, but not always, found. Deafness is frequently found.

Encephalitis in Diphtheria.

VERA DOLGOPOL AND SELIG KATZ (*American Journal of Diseases of Children*, April, 1950) describe the occurrence of encephalitis in five children dying of diphtheria. They state that most often diphtheritic damage to the nervous system takes the form of peripheral neuritis, but there have been reports of cerebral hæmorrhage or embolism from heart thrombi, meningitis due to *Corynebacterium diphtheriæ*, and degeneration of ganglion cells and nerve tract, more often in the subtentorial and spinal regions than in the cerebrum. The authors report clinical and autopsy findings in five patients who showed encephalitic changes. Four were children and one a young adult. In four the diphtheria was of the malignant nasal and faucial type with bull-neck œdema, and in one the disease was tonsillar, tracheal and pulmonary, being due to an organism of the toxic *mitis* type. Only one patient had pronounced clinical evidence of neurological involvement. He had severe mental depression and then peripheral neuritis with paralysis of respiratory muscles and death from respiratory failure. One other patient had mental confusion and disorientation shortly before dying of cardiac failure. The other deaths were from cardiac failure or diphtheritic pneumonia. The histological evidence of encephalitis varied. Perivascular cuffing was severe in four cases and minimal in one. Glial nodules were seen in three, in one of them with neuronophagia. These changes were seen in grey and white matter of

cerebrum and medulla. Cellular degeneration was only moderate and occurred in medulla, mid-brain and thalamus. There was central chromatolysis, with preservation of the Nissl substance on the periphery of the cells and an eccentric location of the nucleus. In the one case of long-standing illness (forty-five days) there was vacuolation of the cytoplasm in some of the cells of the thalamus. The myelin was intact in the cerebrum, medulla, cerebellum and roots of the cranial nerves. In the patient dying of respiratory failure, the intercostal nerves showed loss of myelin. Pronounced rise in the protein content of the cerebro-spinal fluid in diphtheritic paralysis and in acute diphtheria without paralysis has been reported occasionally, but in all cases the cell content was not increased.

ORTHOPÆDIC SURGERY.

Oblique Displacement Osteotomy for Osteoarthritis of the Hip Joint.

G. V. OSBORNE AND W. H. FAHRNI (*The Journal of Bone and Joint Surgery*, May, 1950) point out that the hip joint acts on a lever principle, the weight of the body at one end of the lever being counterbalanced by the pull of the abductor or anti-gravity muscles at the other end. The head of the femur, being the fulcrum, is subjected to a summation of these forces. Experimental evidence is advanced to show that the joint pressure, when weight is taken with the hip in abduction, is twice the body weight; when the hip is in mid-position, the joint pressure is two and a half times the body weight; when the hip is in adduction, the joint pressure is three times the body weight. The authors consider that this increased load when the hip is fixed in an adducted position is responsible for the unrelenting progress of osteoarthritis in a hip that has entered into the stage of deformity. Experiments show that after displacement osteotomy, if the distal fragment of the femur lies in contact with the pelvis, all the body weight is transmitted through the pelvis, and there is no joint pressure at the hip. When this displacement is obtained, the distal fragment lies in contact with the under-surface of the transverse ligament of the acetabulum, and the lesser trochanter lies against the inferior ramus of the ischium. The authors have reviewed the end results in a series of 75 patients treated by this operation. Pain was relieved in 81% of cases. The average shortening was just less than one inch. In 95% of the successful cases a solid check to adduction was encountered at or about the neutral position. The authors state that in no clinically successful case reviewed has there been radiographic evidence of progress of the arthritis. There have in fact been many examples of partial restoration of joint space. In 14 cases pain was not relieved by the operation; without exception in these cases the block to adduction movement, which is the index of pelvic support and the criterion of a successful mechanical result, was absent; radiographic examination confirmed that adequate displacement had not been achieved. In seven cases the failure to secure adequate displacement was explained easily from among four causes: (i) local fibrosis due to previous operations—three cases; (ii) a long inner spike on the distal fragment due to splintering of the neck—two cases; (iii) calcification in the psoas tendon—one case; (iv) extreme obesity causing inadequate immobilization with slipping back of the distal fragment—one case. In the other five cases no reason for the technical failure was evident. Three patients who were relieved of symptoms failed to show either a block to adduction or radiologically adequate displacement. It was considered that this apparent anomaly was due to correction of deformity and prolonged rest in plaster. The authors consider that the beneficial effect of displacement osteotomy in osteoarthritis of the hip is due, firstly, to correction of deformity and secondly, to the bone block effect of the displaced shaft, which prevents the further development of the adducted position and may act as a pelvic support. The principles and technique of the operation are described fully.

Posterior Exposure of the Hip Joint.

ALEXANDER GIBSON (*The Journal of Bone and Joint Surgery*, May, 1950) states that the advantages of the posterior approach are that it is rapid, almost bloodless and attended by little shock. The power of the muscles is unimpaired, for they are not detached from an extensive iliac origin. The *gluteus maximus* and *tensor fasciæ latæ*, which are so important for stability of the hip, are not weakened and the operation causes no instability. The original purpose of this exposure, as used by Langenbeck, was to secure drainage in suppurative arthritis. In Kocher's hands it was employed to give full and free access to the acetabulum in the surgical treatment of tuberculosis of the hip joint. In modern surgery it has a still wider field of usefulness. In posterior fracture-dislocations of the hip joint, direct exposure of the site of the injury is gained. When operation is required to secure replacement of a slipped upper femoral epiphysis the posterior part of the joint with the displaced epiphysis is exposed readily. The approach is ideal for exposure of the sciatic nerve in the buttock, and for dealing with injuries of the gluteal arteries. In arthrodesis of the hip joint the anterior flap may be retracted to allow access to the ilium, which may be required for use as a graft, and the field of implantation of the graft is displayed with the least possible trauma. In cup-arthroplasty of the hip joint the simplicity and efficacy of the method give the most useful application of all. The author considers that it is not too much to say that as a routine procedure for exposure of the hip joint the posterior approach is *facile princeps*.

Pseudarthrosis of the Hip Joint.

R. G. TAYLOR (*The Journal of Bone and Joint Surgery*, May, 1950) has reviewed the results in 93 patients who have had the head and neck of the femur excised for various diseases of the hip. The results were good in 83 cases and poor in seven cases. Three patients died as a result of the operation. The author considers that pseudarthrosis is the most satisfactory and the most reliable operation (i) in ankylosing spondylitis, and (ii) for patients over sixty years of age with disabling osteoarthritis. The more formidable operation of cup-arthroplasty may prove to be superior for younger patients with osteoarthritis. The author states that the best results so far obtained in bilateral osteoarthritis are those in which arthrodesis was performed on one side and pseudarthrosis on the other. Only one patient with rheumatoid arthritis has been operated upon. The result was unsatisfactory owing to the polyarticular nature of the disease. Pseudarthrosis is probably not advisable in this disease. The author discusses the technique of operation and post-operative management.

A Walking-Plaster Appliance.

D. G. WRIGHT (*The Lancet*, November 11, 1950) describes a walking-plaster appliance that is applied over the plaster like a shoe and can be removed when the patient goes to bed or as required. It is made of hard rubber with a core of asbestos. The front, sides and back are vertical and continuous, apart from four slits that pass downwards from the upper edge to terminate an inch from the sole. The two front slits allow the front to be hinged down like a tongue, and with the two other slits, one in each side wall, allow the sides to be drawn together over the tongue with a leather lace. The sole is rigid and has a flat upper surface; the lower surface is appropriately curved and is fitted with a non-skid tread. A range of sizes has been devised. The author describes the orthopædic and utilitarian advantages of the appliance and its mechanism.

Restoration of Function of the Hand.

W. C. GRAHAM, J. B. BROWN AND B. CANNON (*Archives of Surgery*, July, 1950) report four cases of digitization of the first metacarpal for restoration of hand function. In two cases both hands were involved. The authors state that it is essential that the cleft be of adequate depth to allow grasping of objects. The tip of the first metacarpal should be directed toward the head of the third metacarpal to produce a finer grasp and a more firm pinch. The first metacarpal may be elongated to equal the third by transplanting a portion of the second joint to it or by bone grafting. The authors consider a lobster-claw type of hand with sensation far more useful than a prosthesis; this is especially true for patients with poor vision.

Medullary Nailing of the Femur.

D. M. STREET (*The Journal of the American Medical Association*, June 24, 1950) presents a comparative study of skeletal traction, dual plating and medullary nailing in treatment of fractures of the femoral shaft. He reviews the history of treatment of these fractures and reports his own results with various methods. He states that although the series was small, the evidence obtained indicates that the processes of fracture healing are not significantly disturbed by methods of internal fixation. Anatomical and functional results are better than with skeletal traction. Time spent in hospital and total disability are least with medullary nailing, which is recommended as the treatment of choice in suitable fractures of the femoral shaft where operative facilities permit.

Special Abstract.

HUMAN MILK.

A REPORT recently issued by the Medical Research Council sets out the results of an investigation by S. K. Kon and E. H. Mawson into the constitution of human milk. The report was completed towards the end of 1947. The work which it records was carried out during the war years of 1941 to 1945, and involved the organization of three dietary surveys and the collection and analysis of single specimens of milk from more than 2000 nursing mothers. In view of the lack of information available on the composition of human milk and also because of the particular interest attached to an investigation related to the dietetic difficulties of wartime, the main points are set out here.

The object of the investigation was to determine how far the content of certain vitamins and other substances in human milk reflects the state of nutrition of the mother with regard to these factors, and to study the influence of wartime dietary changes. Since different populations differ in their food habits, samples of milk were obtained from more than one locality. Samples of full lactation milk were collected in Reading, a prosperous country town, and in Shoreditch, a working-class district of London. Special series of early lactation samples were obtained through a number of different hospitals and through private practitioners and nursing homes. The constituents studied included vitamin *A*, carotenoids, vitamin B_1, riboflavin, ascorbic acid, fat, solid-not-fat and, in a proportion of samples, lactose, total nitrogen, calcium and phosphorus. One or more of these was measured in each of 2284 samples of milk. In addition to the dietary influences the following relevant factors were studied: the time of day, the stage of lactation, the milk yield, the age of the mother, and her parity. Some of the main quantitative findings have been set out in a table for convenient reference.

The Fat Content.

No consistent variation in the fat content of milk was observed between the third and the twenty-fourth weeks of lactation, nor was there any difference with variations in milk yield. The fat content of Reading samples obtained between 1942 and 1945 (4·78 grammes per 100 millilitres) was higher than that of Shoreditch samples obtained during the same period (3·91 grammes per 100 millilitres). No difference from year to year was found at either place. Available evidence does not provide an explanation of the differences observed between Reading and Shoreditch. Possible explanations include differences in the fat content of the diet and undetected sampling errors.

The Solids-Not-Fat Content.

The solids-not-fat content of milk remained constant during the years 1942 to 1945, and there was no difference between Reading and Shoreditch. The mean value for both was in the vicinity of nine grammes per 100 millilitres. The solids-not-fat content decreased slowly with the progress of lactation.

The lactose content increased slightly during the first weeks of lactation and remained almost constant thereafter. There was no difference between Reading and Shoreditch values (approximately 6·95 grammes per 100 millilitres).

The total nitrogen content fell rapidly during the first three or four weeks of lactation and then gradually; values were the same at both places (approximately 240 milligrammes per 100 millilitres at the third week of lactation, falling to approximately 190 milligrammes per 100 millilitres at the twenty-first to twenty-fourth week of lactation).

Values obtained for calcium (29·9 milligrammes per 100 millilitres) and phosphorus (13 milligrammes per 100 millilitres) agree with those of other workers.

The Biological Value of the Proteins.

The biological value of the proteins of freeze-dried milk, measured on rats by the method of Mitchell, proved very similar to that simultaneously obtained for freeze-dried cow's milk.

The Vitamin A and Carotenoid Content.

From results believed to be relatively free from sampling errors, it was found that with increasing fat content the vitamin *A* and carotenoid content of milk increased, but the concentration in the fat decreased. Diurnal variations in the vitamin *A* content of the milk fat were small; those for carotenoids were somewhat greater. Results for samples taken during three successive weeks showed much less variation between samples from the same woman than between samples from different women.

The vitamin *A* content of milk fat was high at the beginning of lactation (greater than 100 international units per gramme on the third and fourth days) and fell rapidly to 46 international units per gramme of fat in the third week. This was followed by a further more gradual decline to 30 international units per gramme of fat at the eighteenth week. After this, slightly higher values were observed. The mean value corrected to the seventeenth week of lactation was approximately 32 international units per gramme of fat.

The carotenoid content of milk fat fell from more than 20 microgrammes per gramme of fat on the third or fourth day of lactation to 4·3 microgrammes per gramme of fat in the third week. In the fourth and subsequent weeks mean values ranged around 3·6 microgrammes per gramme of fat.

Women whose milk yield was considered low produced milk fat with a significantly higher vitamin *A* and carotenoid concentration than that shown by the general means. Those whose milk yield was considered high produced milk with the same vitamin *A* and carotenoid content as the general means. The concentration of vitamin in milk fat increased with increasing age of the mothers, and a similar, though smaller, change took place with carotenoids. No consistent variations with parity were found. In a special study with one woman it was found that administration of vitamin *A*, but not of an equivalent quantity of carotene, raised the vitamin *A* content of her milk. The milk of 22 women who had consumed liver within twenty-four hours of the taking of the sample, had a vitamin *A* content of much higher than the general means. The administration of large doses of vitamin *A*, both immediately before and after parturition, led to the secretion of milk much richer in vitamin *A* than that normally produced.

The proportion of carotenoid pigments remained relatively constant throughout lactation, and no difference was found with change in season of the year. Examination of milk and blood plasma taken from three women indicated that carotene passed through the mammary gland only with difficulty. There was no correlation between the content of vitamin *A* in plasma and that in milk fat, but there was a significant correlation for carotenoids. No seasonal variation was found in the content of vitamin *A* in milk fat. That of carotenoids tended to be lower in January and February than during the rest of the year. So far as could be ascertained, the supplement of cod liver oil given to pregnant women from April, 1943, onwards had no influence on the vitamin *A* content of the fat of milk which they later produced.

The Vitamin D Content.

The vitamin *D* content of five pooled samples of early lactation milk fat, measured by biological tests, varied between 0·13 and 0·27 international unit per gramme. That of three similar samples collected in later lactation varied from 0·15 to 0·41 international unit per gramme. Low values were found for samples collected during the winter months.

The Vitamin B_1 Content.

The proportion of "free" to total vitamin B_1 in milk increased with the progress of lactation. Diurnal variations in the vitamin B_1 content of milk were small. Variations from week to week were slightly greater. The vitamin B_1 content was low initially (three microgrammes per 100 millilitres on the third day) and rose rapidly during the first three weeks. From the fifth week onwards it remained almost constant at about 17 microgrammes per 100 millilitres. In women producing limited quantities of milk, it was below the normal during the first nineteen weeks of lactation, but normal thereafter. It did not vary consistently with the age of the mother. In early lactation the milk of *multiparæ* contained more vitamin B_1 than that of *primiparæ*. Possible nervous influences on the vitamin B_1 content are discussed, but no clear conclusions are drawn from the available data.

The giving of large doses of the vitamin (9 to 15 milligrammes daily) caused considerable immediate increases in the vitamin B_1 content of milk in both early and later lactation. This increase was chiefly in the "free" (non-phosphrylated) form. Analysis of 790 samples of milk from Reading women showed an increase from 14·7 microgrammes per 100 millilitres in 1941-1942, when white bread was

available, to 18·3 microgrammes per 100 millilitres in 1944-1945. National wheatmeal bread was introduced at the end of the period 1941-1942. None of the 359 Shoreditch samples was examined before the change, but subsequent trends were the same as those at Reading. Although large doses of vitamin B_1 caused an immediate considerable increase in the vitamin B_1 content of milk, smaller increases in the vitamin B_1 content of the diet apparently led to only small and very gradual increases. If values for the vitamin B_1 content of milk obtained in different countries are comparable, the values in Britain at the time when white bread was eaten are similar to those found in the United States. Those obtained after the introduction of national wheatmeal bread were higher, and also higher than those found in Australia.

The Riboflavin Content.

The riboflavin content of milk undergoes pronounced fluctuations related to the riboflavin consumed in meals, and allowance for this had to be made in the collection and the assessment of samples. Results for early lactation samples taken between 1.30 p.m. and 2.30 p.m. suggest that the riboflavin content of milk does not change greatly during the first seventeen days of lactation. Doses of three milligrammes of riboflavin given three times a day to each of nine women caused up to tenfold increases in the riboflavin content of the milk. There was no indication of a "ceiling" value as for vitamins B_1 and C. With one woman a single dose of three milligrammes of riboflavin was followed by an immediate rise in the riboflavin content of the milk and a similar change in urinary excretion. A dose of one milligramme had a smaller effect. The administration of riboflavin caused a much smaller increase in the riboflavin content of milk of women between the fourth and tenth days of lactation than in that of women in established lactation. The reason for this is not known. The riboflavin content of milk remained fairly constant at Reading at about 26 microgrammes per 100 millilitres between April, 1942, and September, 1944. In the fourth quarter of 1944 and the first quarter of 1945, the figure dropped, possibly in relation to a current decrease in the riboflavin content of flour. No seasonal variation was found in the riboflavin content of the milk.

The Vitamin C Content.

The diurnal variation of the vitamin C content of milk is extremely small. Variation from week to week may be considerably greater with changes in the vitamin C content of the diet. A dose of 50 milligrammes daily of vitamin C given to each of 10 mothers, at a time when the vitamin C content of milk was low, produced moderate increases in the course of the two weeks. A study was made of the vitamin C actually consumed by 16 mothers, and the amount of vitamin C secreted into the milk. Principal sources of vitamin C in the diet included oranges, leafy vegetables and, to a less extent, potatoes and cow's milk. The daily vitamin C intake varied from 44 to 106 milligrammes. With the lower intakes a high proportion was secreted into the milk, in four cases only 17 or 18 milligrammes daily being left for the mother's own needs. This partition was also influenced by the milk yield.

Pronounced seasonal variations were observed in the vitamin C content of milk. These were apparently related to the availability of green vegetables and the seasonal changes in the vitamin C content of potatoes. They were modified when oranges were imported. The yearly mean values for the vitamin C content in milk increased between 1941 and 1945, probably because of increased consumption of green vegetables, improved methods of cooking and, in later years, consumption of imported citrus fruit. Values observed at Shoreditch differed but little from those at Reading despite the fact that many Reading women had vegetables from their own gardens or allotments.

The Composition of Milk Throughout an Individual Lactation.

Complete records were kept of all food consumed daily in a lactation which lasted for thirty-three weeks and during which 81 samples of milk were analysed for the same constituents as in the main investigation. By taking advantage of the special supplements for lactating women, this mother obtained a high proportion of, or all, the recommended intakes of nutrients. The fat content of the milk was unusually low, but apart from that the milk was of better than average quality. The changes in composition with the stage of lactation, or occasioned by alterations in the dietary intake, were the same as found for separate samples from large numbers of women. In a period during which the consumption of vitamin C was voluntarily restricted, the vitamin C content of the milk decreased greatly.

Dietary Studies.

Three dietary surveys were carried out by two methods with 109 Shoreditch women whose milk was examined. The results were substantially similar. The following approximate daily intakes of nutrients were found: Calories 2400 to 2500, protein 88 grammes, fat 96 grammes, carbohydrate 300 grammes, calcium one gramme, iron 14 milligrammes, vitamin A 2000 international units, carotene 800 international units, vitamin B_1 1·4 milligrammes, vitamin C 30 to 60 milligrammes. These values are lower than the recommended allowances of the United States National Research Council and the standards of the League of Nations. Full advantage was not taken of the rationed foodstuffs to which lactating women were entitled. The results for 21 women, who measured the food which they consumed during two separate weeks, showed that for all nutrients except vitamin A the same result was obtained irrespective of the week chosen. There was very little correlation between the vitamin content of the milk and that of the diet within any of the three surveys, or between surveys. One survey, however, can be conveniently divided into three periods, when the mean values for the content in milk of all vitamins, except vitamin C, follow the same trend as in the diet.

A Comparison Between Glasgow and Shoreditch.

A comparison was made in 1945 of the milk of 47 Glasgow women with that of 37 Shoreditch women. The two groups were comparable in financial circumstances, age and parity of the mothers, and birth weights of the babies. Sampling errors made the results for riboflavin and fat content difficult to interpret. The vitamin B_1 content, 16 milligrammes per 100 millilitres, was nearly the same in both places. The vitamin C content was only 3·1 milligrammes per 100 millilitres at Glasgow, as compared with 3·9 milligrammes at Shoreditch. The vitamin A content was 40 international units per gramme of fat at both places, but the carotenoids were 5·4 microgrammes per gramme of fat at Glasgow, as compared with 3·8 microgrammes at Shoreditch. The content of solids-not-fat was slightly higher at Shoreditch, but the difference was not statistically significant.

Milk Composition in Relation to Nutritional Requirements.

The authors discuss the requirements of the infant and the additional needs of the nursing mother in the light of the composition of mother's milk as established in the present study. Surveys show that many Shoreditch women failed to obtain the allowances of nutrients recommended by either the League of Nations or the National Research Council of the United States of America. Although measurements of food intake were not made at Reading, the milk results suggest that the mean consumption of vitamins there was not greatly in excess of that of Shoreditch. On the other hand, the intensive study of individual lactation shows that, by making use of the special supplements, a mother could, despite rationing, maintain throughout lactation at least the standards of the League of Nations, and for some nutrients even the higher allowances of the National Research Council. The failure of the majority of lactating women to achieve this may have been due to unwillingness to change dietary habits, to the sharing of the special supplements with others, or to economic causes. The authors' opinion is that cost was not necessarily the primary factor. Although a difference in milk yield between the high and low income groups cannot be entirely excluded, it would appear that a higher family income did not make it possible for women to produce milk with a vitamin content above the average level.

The authors examine the vitamin requirements of infants in the light of their provision in human milk and cow's milk. They state that the breast-fed infant is favoured in its supply of vitamin C, and in winter of vitamin A, but the bottle-fed child receives more vitamin B_1 and riboflavin. Though the two milks supply similar quantities of vitamin D, it is well known that the danger of rickets is greater with the artificially fed baby, and it is primarily for him that special supplements of cod liver oil and orange juice have been provided. The mechanism for secreting vitamin A into milk is such that, unless the mother's vitamin A reserves are low or exhausted and her diet grossly deficient in this factor, the infant is unlikely to suffer from shortage. The diets of many women investigated appeared to be

below the optimal level in vitamin *A* content, but the intake of the infants would appear to be adequate.

The authors' results indicate that there is very little vitamin *D* in milk, and the daily intake by breast-fed infants is unlikely to exceed 20 international units. The frequent inadequacy of vitamin *D* content, with a resultant occurrence of rickets among breast-fed infants, is, it is suggested, a penalty of civilization as, under more natural conditions of exposure to light, mother's milk would contain more vitamin *D*, and the infant would synthesize it for himself. The current policy of the Ministry of Health is to encourage the administration of cod liver oil to all infants, and it appeared that this was being largely carried out by the mothers.

The vitamin *C* consumption of the majority of the mothers whose milk was examined was probably unsatisfactory as judged by the standard of the United States National Research Council, but the results indicate that the vitamin *C* intake of the infants must have reached the amount recommended by the same authority. The authors' view is that attention should be directed to the vitamin *C* nutrition of the mother rather than to that of the child. If the mother's diet contains adequate amounts of this factor the child is bound to obtain enough.

Despite the low vitamin B_1 content of human as compared with cow's milk, infantile beriberi is a very rare condition, and it seems probable that requirements of the breast-fed infant for vitamin B_1 are very small. Owing to the compulsory use of high extraction flour in Britain, the consumption of vitamin B_1 has been greater during the latter part of the war than previously, and consequently breast-fed infants have also obtained more of this substance than before.

Only a small amount of riboflavin is obtained by breast-fed babies as compared with those fed on cow's milk. Very little is known concerning the riboflavin requirements of infants and the allowance suggested by the United States National Research Council could not be met from human milk. However, this quantity is easily obtained from cow's milk.

Conclusion.

In the preface to the report the following special points are mentioned:

1. It has always remained perfectly possible for an intelligent mother to obtain a fully satisfactory diet, and though surveys in one of the poorer districts of London showed in fact that many women failed to do so, no changes attributable to malnutrition were ever detected in their milk. It must be remembered, however, that the conditions of the experiment would tend to exclude the worst nourished and most careless mothers, and that the first effect of malnutrition on the milk is probably to diminish the amount secreted and thus bring into operation compensatory mechanisms, which may mask reductions in the contents of individual constituents.

2. The law governing secretion into milk of the different vitamins must vary widely, and the new material contained in this report only underlines how obscure many of the physiological problems of lactation remain and how misleading it may be to apply to human milk conclusions drawn from the study of cow's milk.

3. Some of the authors' observations have considerable practicab'e importance: notably the conspicuous and sustained rise in the vitamin B_1 content of the milk following the introduction of national wheatmeal bread; the similar rise in the vitamin *C* content after the distribution of a consignment of oranges, showing that vitamin *C* supplements if taken by the mother rather than the infant will benefit both parties instead of only one; and the demonstration that doses of vitamin *A* given during pregnancy were without effect on the milk subsequently produced.

4. This report forms the most comprehensive attempt so far to assemble average values for the constituents of human milk.

Correspondence.

BIBLIOGRAPHY OF DR. BEANEY.

SIR: The Honourable Mr. Justice J. A. Ferguson, of Sydney, has discovered in his collection an old Melbourne medical journal containing an article by James G. Beaney, F.R.C.S. The journal is *The Medical and Surgical Review (Australasian)*, edited by "James Keane, Late Surgeon of The West London Hospital". The article by Beaney is entitled "A New Method of Treating Acute Orchitis, as Suggested by its Pathological Condition". The paragraph describing the treatment reads as follows:

> When called to a patient suffering from orchitis, and complaining of intolerable pain, I direct him to stand erect, and grasping the organ, as I would in a case of hydrocele, I plunge in a trochar and canula into the tunica vaginalis at the bottom, and most depending part of the scrotum, and completely evacuate it. I then direct him to keep his bed, and apply a lotion of acetate of lead and opium, this generally effects a cure in six or seven days.

The article is marked "To Be Continued".

Apart from the article by Beaney, the journal is noteworthy as being an early attempt at the formation of a medical journal. The issue is Volume I, Number 1, March, 1863. The publisher was F. F. Bailliere, who, it will be remembered by readers of the writer's article, "The Egregious Dr. Beaney" (THE MEDICAL JOURNAL OF AUSTRALIA, May 6, 1950, page 593), was at one time Beaney's intimate friend and publicity agent and later his enemy. The journal was to be published monthly and the annual subscription was £1 1s. The journal is divided into sections. Firstly, there are original articles. There are four articles—by W. McCrea, James T. Rudall, James G. Beaney, and James Keene respectively. Then there is a section of reviews, which is followed by "Monthly Retrospect", correspondence, medical news, vital statistics and answers to correspondents. At the end there are sixteen pages of advertisements for medical and scientific works which could be bought from F. F. Bailliere, "Scientific Book Importer and Publisher". Amongst these advertisements is a small section on Australiana, and collectors will be interested to know that Matthew Flinders's "Voyage" with the volume of plates was offered at five pounds. In the "Monthly Retrospect" it is noted that the mortality from ovariotomy had greatly dropped. Spencer Wells had reported 56 cases with only 18 deaths.

Taking it all in all, this is a very interesting journal, and one wonders if one's estimate of the characters of Beaney and Balliere should not be revised. It cannot be doubted that they were eager, thrusting and to some extent unscrupulous men, but they certainly must have influenced contemporary thought and practice.

It would be very interesting also to know if any other later copies of this journal are known to exist.

Yours, etc.,

C. CRAIG.

General Hospital,
Launceston,
November 1, 1950.

ERYTHROBLASTOSIS FŒTALIS, OR HÆMOLYTIC DISEASE OF THE NEWBORN, AND SIX HEALTHY, NORMAL BABIES.

SIR: Mrs. S.B., aged twenty-nine years, has had eight children. She is of blood group B and Rh-negative, and her husband is of group B and Rh-positive. She has never had a blood transfusion. Her obstetrical history is as follows.

1. Her first child was a boy, belonging to blood group B and Rh-positive; he was normal at and after his birth in 1938.

2. Her second child, also a boy, belonged to blood group O and was Rh-positive; he was normal at and after his birth in 1940.

3. In 1941 the patient had a stillbirth at term. She says that "the baby came away in pieces".

4. A third male child was born in 1943; he belonged to blood group B and was Rh-positive. Labour was not induced. The child was "very delicate" immediately after birth and until he was some weeks old. One blood transfusion was given to him when he was two days old.

5. A fourth male child, belonging to blood group O and Rh-positive, was born in 1945. He was given a blood transfusion immediately after birth and another when he was two weeks old.

6. On January 4, 1948, the patient was delivered of a stillborn female child at term; the appearance was typical of *hydrops fœtalis*.

7. On December 23, 1948, the patient was delivered of a male child, of blood group B and Rh-positive, after surgical induction of labour at about the thirty-sixth week of pregnancy. The child's blood reacted strongly to the Coombs test, and other tests indicated the necessity for an exchange blood transfusion; this was given to him by Dr. A. E. Shaw immediately after birth. It is interesting to observe that on July 21, 1948, the serologist had reported: "No antibodies detected." On October 30, 1948, the report had read: "Rh_0 blocking antibodies present, titre 2." On December 7, 1948, the report had read: "Rh_0 blocking antibodies, titre 2."

8. On October 23, 1950, a female infant, of blood group B and Rh-positive, was born after surgical induction of labour at about the thirty-sixth week of pregnancy. On July 3 the serologist had reported as follows: "Rh (D) blocking antibodies—titre of ± 512 detected." On September 6 the serological report was: "Rh_0 (D) blocking antibodies to titre of 64 (± 128)." Examination of specimens taken on August 3 and September 6 gave identical results. After this drop in the antibodies, a most gloomy prognosis was given by the serologists. However, the baby cried lustily immediately after delivery, was quite vigorous and did not require resuscitation. She weighed five pounds eleven ounces, but had a few petechial spots on the right side of her forehead. The result of the Coombs test was reported as being only faintly positive; but the serologist, Dr. J. Dique, considered that an exchange transfusion was indicated, and he accordingly gave it to her. She was severely distressed during the exchange transfusion and required resuscitation with oxygen. She has done well since.

An interesting obstetrical history is given. All the babies were Rh-positive, although some belonged to group B and others to group O. The third fœtus may have been affected by *hydrops fœtalis*, and the sixth presented a typical example of that condition. The sequence of two normal pregnancies followed by six in which *erythroblastosis fœtalis* was present is typical. This case would seem to stress the following points.

1. The necessity for the closest clinical observation of these patients, ensuring induction of labour at the most favourable time. When menstruation is irregular, as in the present case, one must be guided by one's judgement of the size of the fœtus and of the comparative "ripeness" of the cervix.

2. The necessity for the closest collaboration between obstetrician and serologist. While the exchange transfusion has saved and will save many lives, and is in our present state of knowledge the only answer to severe erythroblastosis, it is anything but the perfect answer. It must necessarily cause tremendous shock to the newborn. The perfect answer will obviously be some substance which can be administered simply to the mother during her pregnancy, if erythroblastosis is suspected—a substance which will be perfectly harmless to her, and which will be more attractive to the Rh antibodies than are the fœtal red cells. However, until such a substance has been discovered, we must indeed be grateful for exchange transfusion.

3. The fact that erythroblastosis, even after it has produced *hydrops fœtalis*, is not necessarily an indication for sterilization of affected women. Thus I believe that Mr. and Mrs. S.B. will produce babies which will not require replacement transfusion, and probably not a transfusion of any kind. It seems to me that her repeated pregnancies have, in some way which is difficult to comprehend, gradually broken down her reaction to the Rh factor.

4. The need for young Australian couples like Mr. and Mrs. S.B. to be provided with furnished homes on a hire-purchase plan. They should also be paid an adequate amount—say two pounds—per child per week until each child has attained the age of eighteen years.

In conclusion, I should like to pay tribute to the skill of the Brisbane serologists, Dr. A. E. Shaw and Dr. J. Dique, without whose cooperation these gratifying results could not have been achieved.

Yours, etc.,

J. M. O'CONNOR.

National Mutual Building,
293 Queen Street,
Brisbane.

November 9, 1950.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED NOVEMBER 11, 1950.[1]

Disease.	New South Wales.[3]	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.[3]	Australian Capital Territory.	Australia.[3]
Ankylostomiasis	*	..	..	..	..	..	..	..	..
Anthrax	*	..	..	..	..	..	..	..	..
Beriberi	*	*	*	*	*	*	..	*	..
Bilharziasis	*	..	..	..	..	..	..	..	..
Cerebro-spinal Meningitis	..	1(1)	1	2(2)	..	3(2)	..	..	7
Cholera	..	..	..	..	..	..	..	..	..
Coastal Fever(*a*)	*	*	..	*	*	*	*	*	..
Dengue	*	*	*	*	*	*	..	*	..
Diarrhœa (Infantile)	..	..	2(1)	..	..	..	..	..	2
Diphtheria	..	4(4)	3(2)	1	5(4)	..	..	..	13
Dysentery (Amœbic)	*	1	..	..	1	..	..	..	2
Dysentery (Bacillary)	*	..	6(5)	..	..	..	*	2	8
Encephalitis Lethargica	..	..	..	..	..	..	..	..	..
Erysipelas	*	*	*	..	*	*	..	..	..
Filariasis	*	..	..	..	..	..	..	..	..
Helminthiasis	*	..	*	*	*	*	*	*	..
Hydatid	*	1	*	*	..	*	*	..	1
Influenza	*	*	*	..	*	*	..	*	..
Lead Poisoning	*	*	..	*	*	*	*	*	..
Leprosy	..	..	..	..	4	..	..	..	4
Malaria(*b*)	*	..	1	..	..	..	..	..	1
Measles	*	*	*	417(178)	*	*	..	..	417
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	..	2	5	9(1)	2(2)	1	..	1	20
Psittacosis	*	..	*	..	*	*	*	*	..
Puerperal Fever	..	..	..	2(2)	..	..	..	..	2
Rubella(*c*)	*	*	..	*	..	*	..	..	..
Scarlet Fever	..	20(11)	23(22)	8(4)	8(4)	1	..	..	60
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	*	..	..	*	*	*	*	*	..
Trachoma	*	..	*	*	*	*	*	*	..
Tuberculosis(*d*)	..	10(9)	18(15)	2(1)	13(10)	3(1)	..	..	46
Typhoid Fever(*e*)	..	..	..	..	..	..	..	..	..
Typhus (Endemic)(*f*)	..	..	..	..	1	..	..	..	1
Undulant Fever	..	..	..	..	1(1)	..	..	..	1
Weil's Disease(*g*)	*	*	1	*	*	*	*	*	1
Whooping Cough	*	*	*	6(3)	*	*	..	..	6
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] The form of this table is taken from the *Official Year Book of the Commonwealth of Australia*, Number 37, 1946–1947. Figures in parentheses are those for the metropolitan area.
[2] Figures not available.
[3] Figures incomplete owing to absence of returns from the Northern Territory and New South Wales.
* Not notifiable.
(*a*) Includes Mossman and Sarina fevers. (*b*) Mainly relapses among servicemen infected overseas. (*c*) Notifiable disease in Queensland in females aged over fourteen years. (*d*) Includes all forms. (*e*) Includes enteric fever, paratyphoid fevers and other Salmonella infections. (*f*) Includes scrub, murine and tick typhus. (*g*) Includes leptospiroses, Weil's and para-Weil's disease.

Obituary.

PAUL TILLETT.

WE regret to announce the death of Dr. Paul Tillett, which occurred on October 31, 1950, at sea.

ARTHUR ERNEST PANTING.

WE regret to announce the death of Dr. Arthur Ernest Panting, which occurred on November 5, 1950, at Adelaide.

JOHN EDWIN BATEMAN.

WE regret to announce the death of Dr. John Edwin Bateman, which occurred on November 20, 1950, at Adelaide.

VIVIAN HECTOR LEIGH-BARLOW.

WE regret to announce the death of Dr. Vivian Hector Leigh-Barlow, which occurred on November 21, 1950, at Dee Why, Sydney.

Post-Graduate Work.

POST-GRADUATE COMMITTEE IN MEDICINE OF THE UNIVERSITY OF ADELAIDE.

Courses for Higher Degrees and Diplomas.

THE Post-Graduate Committee in Medicine of the University of Adelaide will arrange courses suitable for candidates for the M.R.A.C.P., F.R.A.C.S. Part I and F.R.A.C.S. Part II in 1951, provided there are sufficient applicants.

M.R.A.C.P.

The M.R.A.C.P. full-time course will begin on June 4 and continue for three months. It will consist of ward rounds, case-taking, tutorials, lectures in pathology, embryology, psychiatry, neuroanatomy and children's medicine, lecture-demonstrations in radiology, hæmatology and electrocardiography, and viva voces and test questions. The fee will be £31 10s.

F.R.A.C.S. Part I.

The F.R.A.C.S. Part I course, which will consist of lectures in anatomy, applied physiology and the principles of pathology, lecture-demonstrations in histology, and viva voces and test questions, will begin on July 9 and continue for three months. It is designed as a full-time course. The fee will be £31 10s.

F.R.A.C.S. Part II.

Lectures on principles of general surgery will be given on Tuesday and Thursday at 5 p.m., beginning on March 6, and will continue for two months. The fee will be £10 10s.

Further information concerning these courses may be obtained from the Medical Secretary, Institute of Medical and Veterinary Science, Frome Road, Adelaide. Intending applicants for these courses are asked to communicate with the Secretary if they have not already done so.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Lines, Verlie, M.B., B.S., 1950 (Univ. Sydney), Balmain and District Hospital, Balmain.

The undermentioned has been elected as a member of the South Australian Branch of the British Medical Association:

Murphy, Thomas Roy, L.R.C.P. and S., 1932 (Edinburgh), 95 Watson Avenue, Toorak Gardens.

Medical Appointments.

Dr. Frank Kenneth Mugford has been appointed a member of the Medical Board of South Australia.

Dr. Edmund Britten Jones has been appointed President of the Medical Board of South Australia.

Dr. John Ewart Cawte has been appointed Resident Medical Officer for Mental Institutions in the Hospitals Department, Adelaide, South Australia.

Diary for the Month.

DEC. 5.—New South Wales Branch, B.M.A.: Executive and Finance Committee. Organization and Science Committee.
DEC. 6.—New South Wales Branch, B.M.A.: Special Groups Committee.
DEC. 6.—Victorian Branch, B.M.A.: Annual Meeting.
DEC. 6.—Western Australian Branch, B.M.A.: Council Meeting.
DEC. 7.—New South Wales Branch, B.M.A.: Clinical Meeting.
DEC. 7.—South Australian Branch, B.M.A.: Council Meeting.
DEC. 8.—Queensland Branch, B.M.A.: Annual Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney)—All contract practice appointments in New South Wales.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in the Commonwealth can become subscribers to the journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £3 *per annum* within Australia and the British Commonwealth of Nations, and £4 10s. *per annum* within America and foreign countries, payable in advance.